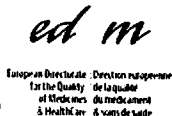


Exhibit 24

**EXHIBIT****Gu (ZHP) 232****Final GMP inspection report**

This final inspection report is issued after assessment of the Company's answers and corrective action plan received on 14th November 2018.

Joint inspection between EMA (AIFA/AEMPS) and EDQM (in the context of the Inspection Programme of manufacturers within the Certification Procedure)

Inspected sites:

Inspected site:

ZHEJIANG HUAHAI PHARMACEUTICAL CO., LTD.

Chuannan, Duqiao, Linhai

Zhejiang 317016, China

From now onwards referred to as: **ZHP Chuannan**

Spot-checks at:

ZHEJIANG HUAHAI PHARMACEUTICAL CO., LTD.

XunQiao, Linhai,

Zhejiang 317024, China

From now onwards referred to as: **ZHP XunQiao**

References:

EDQM: INSP 2018-039-P01

EMA: INS/GMP/2018/070 and INS/GMP/2018/071

Inspection date: 10 – 13 September 2018

Inspectors:

Lead Inspector	Ms Cristina BACCARELLI	ITALIAN MEDICINES AGENCY, AIFA, ITALY
Inspector	Dr Thomas HECKER	EDQM, COUNCIL OF EUROPE
Inspector	Dr Manuel IBARRA LORENTE	AGENCIA ESPAÑOLA DE MEDICAMENTOS Y PRODUCTOS SANITARIOS, AEMPS, SPAIN
Expert	Dr Igor POPOVIC	EDQM, COUNCIL OF EUROPE
Expert	Dr Corina NACHTSHEIM	FEDERAL INSTITUTE FOR DRUGS AND MEDICAL DEVICES, BfArM, GERMANY

Interpreter appointed by EDQM:

Mrs SU, Huili

Observers from local regulatory authority:

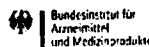
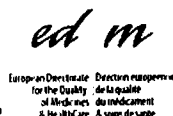
Center for Food and Drug Inspection of CFDA

Ms. WANG, Mengyuan

Drug Inspection Center of Taizhou Market Supervision Administration

Ms. ZHU, Jingjing

Mod. 372/02 – GMP Inspection report	Rev. 0	Date: 8/10/2015	Page 1 of 33
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GOBIERNO
DE ESPAÑAMINISTERIO
DE SANIDAD, CONSUMO
Y BIENESTAR SOCIAL

Introduction / Scope of inspection

The joint EMA/EDQM inspection took place in the context of the EDQM's CEP Procedure and the Article 31 referral procedure according to Directive 2001/83/EC that was triggered after the detection of an impurity, N-nitrosodimethylamine (NDMA), in the Valsartan active substance supplied by several companies to manufacturers which produce some of the Valsartan medicines available in the EU. NDMA is classified as a probable human carcinogen based on the results of laboratory tests. The presence of NDMA was unexpected and is thought to be related to process design or to changes in the way the active substance was manufactured.

The for-cause inspection was aimed to:

- Evaluate the root cause analysis of NDMA contamination of Valsartan
- Assess (potential) NDMA in other sartans
- Examine potential cross-contamination of other APIs by sartans
- Assess potential formation of other nitrosamines
- Check the communication of the Company with national and international authorities

In order to understand the potential root causes of the contamination of active pharmaceutical ingredients that block angiotensin II receptors, further referred to as sartans, the inspection team focused not only on the GMP requirements for APIs as laid down in EU GMP Part II (ICH Q7), but also on the implementation of other ICH quality guidelines, such as:

- Pharmaceutical Development, ICH Q8
- Quality Risk Management, ICH Q9
- Pharmaceutical Quality System, ICH Q10
- The development and manufacture of the drug substance, ICH Q11

To proceed as such was considered as in line with the ICH Q7 Q&A approach that ICH Q7 should be applied in combination with the principles laid down for development and manufacturing in ICH Q11 (see definition of API starting material; see also ICH Q8(R2) Part II), Quality Risk Management (ICH Q9) and Pharmaceutical Quality Systems (ICH Q10).

Zhejiang Huahai Pharmaceutical Co., Ltd. was founded in 1989 and owns different manufacturing sites specialized in production of APIs, intermediates and drug formulations. The four main product categories are ACE inhibitor and sartans, anti-depressant, anti-diabetes and anti-AIDS.

The company has three facilities located in Zhejiang province:

- XunQiao Site & Headquarters (from now on referred to as **ZHP XunQiao**): manufacture of API and finished dosage formulation
- Chuannan site (from now on referred to as **ZHP Chuannan**): manufacture of APIs and API intermediates
- Huanan Site: manufacture of API intermediates



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MINISTERIO DE SANIDAD, CONSUMO Y BIENESTAR SOCIAL

Inspected areas

As outlines above, the inspection was a for-cause inspection and therefore not aimed to cover all GMP relevant areas.

ZHP XunQiao: only documents related to evaluation of potential NDMA/NDEA contamination were reviewed, the site was inspected briefly as no Valsartan production is performed

ZHP Chuannan:

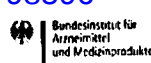
- Pharmaceutical/process development of Valsartan. In this context the team reviewed the firm's approach on the application of risk management principles throughout the life cycle of the API subject to the inspection
- Furthermore, a number of crucial Quality Assurance procedures, such as OOS handling, complaint management, deviation management and change control were reviewed
- In terms of the GMP compliance of the manufacturing areas, the inspection team visited workshops 02 and 13
- In order to evaluate the recovery of solvents as potential source of NDMA contamination, the solvent recovery area in workshop 13 (building no. 14) was inspected
- The company's main storage facilities, warehouses in building 16 and 78 west (both multistorey warehouses), were subject to a brief visit
- Focused on the quality control of Valsartan, Valsartan intermediates and some related raw materials, the team inspected the firms Quality Control facility located in the West zone inside of building no. 52 (HPLC, GC-MS) and building no. 02
- Samples were taken from the retention samples room located on the East zone inside of QC building no. 02
- Weighing room located on the East zone inside of QC building no. 02
- The firm's approach on Valsartan process validation was evaluated
- Cleaning procedures and cleaning records for Valsartan were reviewed

Areas not inspected

All the areas not explicitly mentioned in this report.

Key personnel met during the inspection

Name	Department & Title
Baohua CHEN	President
Jun DU	Executive VP
Jenson YE	Vice President, Quality Assurance, headquarters
Min LI	Analytical Operation, VP, headquarters
Minda CAI	Vice President, Marketing & Sales, headquarters

GOBIERNO
DE ESPAÑAMINISTERIO
DE SANIDAD, CONSUMO
Y BIENESTAR SOCIAL

Jie WANG	Vice President, Business Development, headquarters
Xiaodi GUO	Vice President, Institute of Pharmaceutical Research
Yanhua MENG	General Manager, API operation
Jucai GE	Director, QA, API operation
Linda LIN	RA Director, headquarters
Shiwen ZHANG	Facility Director, Chuannan site East Zone
Peng WANG	Facility Director, Chuannan site West Zone
Baozhen CHEN	Director, Corp. QA
Qiangming LI	Director, QC, Chuannan site
	Director, QA, Chuannan site West Zone
Yuelin HU	Assistant Director, QA, Chuannan site East Zone
Peng DONG	Deputy Director, Chuannan site East Zone
Ms. Yu	Translator
Wayne CHENG	Translator
Ying SONG	QA, Chuannan site East Zone
Mi XU	Director, Marketing & Sales, headquarters
Ting ZHOU	Technical Director, RA, headquarters
Dongqin WANG	Assistant Director, QA, Chuannan site West Zone
Peng DONG	Deputy Director, Chuannan site East Zone
Yuanxun ZHU	Deputy Director, Technical, Chuannan Site West Zone
Yinhua TANG	Assistant Director, QC, Chuannan Site
Jinyi LI	Manager, QA, Chuannan Site West Zone
Liqing XIE	Deputy Manager, Warehouse, Chuannan Site East Zone



Qijun GUAN	Manager, Warehouse, Chuannan Site West Zone
Long HUANG	Workshop Director, Workshop 13
Changli LI	Workshop Director, Workshop W02
Yue ZHU	Supervisor, Engineering Dept., Chuannan Site East Zone
Yan Zhu	Quality Director of Xunqiao API site
Zenghua Zhang	Manufacture Director of Xunqiao API site
Weixing Fan	Engineering Director of Xunqiao API site
Wenfeng Huang	Technical Director Assistant of Xunqiao API site
Xiaohong Zhao	QA Director of Xunqiao API site
Meijiao Zheng	QA Manager of Xunqiao API site

Inspectors findings and observations relevant to the inspection; deficiencies

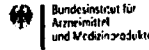
The inspection resulted in nine 'major' and eight "other" deficiencies, summarising a significant number of individual observations.

Critical deviations	Major deviations	Other deviations	Total number of deviations
0	9	8	17

The Major deficiencies were found in the following areas:

1. The investigations conducted in the context of the NDMA/NDEA contamination of Valsartan showed significant flaws;
2. The company's risk assessment performed in the context of the development/implementation of the optimised Valsartan process, conducted in July/August 2018, was not satisfactory; moreover, the company did not identify the need to develop a control strategy to reduce the new risks introduced with the optimised process;
3. Several gaps were identified in the context of the development of the Valsartan process as revised in 2011/2012. N.B.: the changes introduced with this modified process led to the formation of the NDMA impurity;
4. Observations related to the handling of the complaints, with specific focus on the NDMA contamination issue;
5. Management of out-of-specification results;
6. Recall management: no recall was formally initiated to manage the actions related to the contaminated Valsartan batches;

Mod. 372/02 – GMP Inspection report	Rev. 0	Date: 8/10/2015	Page 5 of 33
-------------------------------------	--------	-----------------	--------------

GOBIERNO
DE ESPAÑAMINISTERIO
DE SANIDAD, CONSUMO
Y BIENESTAR SOCIAL

7. Reprocessing/blending operations including traceability of reprocessed/blended material;
8. Data integrity issues in relation to GC-FID analysis;
9. Inadequate investigation of unknown peaks detected in GC-MS analysis of batches of Valsartan manufactured with the new process as optimized in July/August 2018.

Notes:

- The deficiencies are sequentially numbered in this report, for ease of reading. The original deficiency number, as sent to the company on 18 October 2018, is reported in brackets next to each deficiency
- At the end of this report the "Definition of Significant Deficiencies" (according to the "Compilation of Community Procedures on Inspections and Exchange of Information") is provided.

N.B.: the inspection was mainly carried out at the Chuannan site, where Valsartan is produced. It should be noted that some of the deficiencies related to procedures also apply to the XunQiao site because many of the procedures are the same for both sites:

- Deficiencies applicable to both sites: D9 points a, b, c (Major –ex Def. 7) and the "Other" deficiencies D6, D7, D8, D11, D17 (ex Def. n. 11, 14, 10, 12,13)
- One deficiency is specifically referred to the XunQiao site, as clearly indicated in the deficiency itself (D1, ex. Def. 15, Other)

The company was sent the list of deficiencies on 18 October 2018 (see Annex 1).

ZHP XunQiao site

The site covers an area of 241,069 m² with 13 API workshops at the time of the inspection. The size of the plant is about one third of the ZHP Chuannan site.

The site is regularly inspected by the local competent authority and by other Regulatory Authorities (USFDA, KFDA, BGV [Germany], Dusseldorf Authority [Germany], ANVISA, COFEPRIS). The site was last inspected by AIFA in March 2018 for 3 APIs: Enalapril Maleate, Quinapril Hydrochloride, Rivaroxaban. As a result, a GMP certificate covering the APIs subject to the inspection was issued.

For the APIs and intermediates manufactured at ZHP Xunqiao refer to **Annex 2** of this report.

The ZHP XunQiao is divided into an API facility and a finished dosage facility.

No Valsartan API is manufactured at the XunQiao site and no materials are in common between the two sites.

The following observation was raised:

- D1. [Other]** (ex Def. n. 15) - During the review of the risk assessment related to the products manufactured at the XunQiao site (RARC-20180904) and to potential NDMA contamination it was observed that it included only an assessment of the processes carried out at the site but it did not consider any other factors such as the quality of the potable water used during the synthetic step, potential contamination of the raw material TEA, etc.

EU GMP Part II no. 2.21; ICH Q9



N.B.: due to an editing error, D1 (ex Def. n. 15) had been erroneously reported as “Major” in the initial report. Nevertheless Annex 1 of the initial report (list of deficiencies sent to the Company on 18 October 2018) reported the correct classification (“Other”). The classification of the deficiency was updated accordingly in this final report.

Company’s response:

Risk Assessment Report of Nitrosamine Document Number: RARC-20180904-2 Impurities for Huahai’s API’s (Xunqiao Site), was updated (RARC-20180904-2, version 03) to include additional factors, as requested in the deficiency. The assessment concluded that the risk of nitrosamine impurities in products manufactured in the Xunqiao site is very low and that the risk of cross-contamination is under control. For Candesartan the risk of nitrosamine impurities is higher than for the other products and a separate risk assessment was performed (RARA-20181009-1, version 01 – attachment 1g).

Inspectors’ comments: answer noted. This will be reviewed as part of the on-going evaluation of the revisions of the relevant CEP applications submitted by the company.

Additionally to the risk assessment mentioned above, the company performed also risk assessment RARA-20170405 to evaluate potential cross-contamination of workshops in XunQiao site. No criticalities were identified, therefore the Company excluded any NDMA/NDEA contamination risks linked to material and personnel movement between workshops.

Valsartan solid dosage forms are manufactured at ZHP XunQiao site using API Valsartan manufactured at the Chuannan site. Tablets are manufactured and shipped mainly to EU and US. Risk assessments were performed also for finished dosage forms manufacturing. A specific risk assessment was performed to evaluate the potential impact on other solid dosage forms manufactured on same line. Additionally, tests were carried out on the other tablets manufactured on the same line after Valsartan and no contamination was found. The related documentation was not subject of the inspection.

Unused API batches were returned to the Chuannan site. Valsartan tablets that were not delivered to customers were destroyed at ZHP XunQiao site.

With regard to the Valsartan tablets shipped to EU, deviation DF-18022 (15th June) was reviewed. The following actions were implemented:

- Immediate stop of production of the two formulations manufactured at the site, both CMO products
- Any in-process products segregated
- Stop of all shipment
- Immediate notification of international marketing department

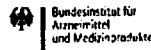
The company sells the solid dosage form to one EU customer, the MAH holder AET - Alfred E. Tiefenbacher (Hamburg, Germany), who was notified after the event. This EU MAH contracts the packaging operations to the following companies, which hold MIAs and carry out batch release of the product in EU:

- G.L. Pharma GmbH (Schlossplatz 1, 8502 Lannach, Austria)
- Genericon Pharma GmbH (Hafnerstrasse 211, A-8054 Graz, Austria)
- Aegis Ltd (17, Athinon Street, Egates, 2643 Lefkosia, Cyprus)
- Biomo Pharma GmbH (Josef-Dietzgen-Str. 3, D-53773 Hennef, Germany)

Four quality agreements between the 3 parties (ZHP – MAH – MIA holder) were in place.

In August the company sent to AET the list of batches shipped and potentially contaminated.

Mod. 372/02 – GMP Inspection report	Rev. 0	Date: 8/10/2015	Page 7 of 33
-------------------------------------	--------	-----------------	--------------

GOBIERNO
DE ESPAÑAMINISTERIO
DE SANIDAD, CONSUMO
Y BIENESTAR SOCIAL

ZHP Chuannan site

The site, put in use in 2005, produces APIs and key intermediates.

The site covers an area of 328,700 m² and it is divided in two separate zones, called respectively East Zone and West Zone; at the time of the inspection there were 36 workshops in operation (18 in each zone, according to the SMF).

The site is regularly inspected by the local competent authority and by other Regulatory Authorities (COFEPRIS, BGV [Germany], AIFA, WHO, USFDA).

The last EU inspection was performed by AIFA in December 2017 for 5 APIs: Ranolazine, Olmesartan Medoxomil, Losartan Potassium, Pregabalin, Nebivolol. As a result, a GMP certificate covering the APIs subject to the inspection was issued.

For the APIs and intermediates manufactured at ZHP Chuannan refer to **Annex 3** of this report.

Quality Management

Some of the deficiencies observed during the inspection in relation to the management of the NDMA/NDEA contamination, risk assessments and root cause analysis, handling of complaints and changes related to Valsartan, can be considered related to the quality management system, which showed not to be robust enough to deal with such an unexpected event.

During the inspection the firm was requested to provide a summary of the events and the subsequent actions. The firm identified a 2011/2012 manufacturing process change as root cause for the NDMA contamination. The process change was based on ZHP's Shanghai R&D laboratory (Shanghai SynCores Technologies Inc.). The laboratory had been requested to perform process improvements studies because a number of issues had been identified within the TEA process, such as:

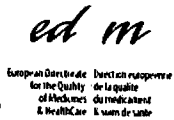
- Long reaction time
- Low conversion rate (yield 40-50%)
- Higher amounts of isomer
- Safety concerns regarding the handling of NaN₃

The studies were summarized in "SC-1141 Valsartan Tetrazole new Process Project Report", which was approved on 20 January 2011. The laboratory studies investigated initially potential improvements of the TEA process, for instance by changing solvent ratios, but this was concluded as not successful because of increased costs and yields still below expectations.

Further studies led to the development of the ZnCl₂ process by changing solvents and reagents (e.g. ZnCl₂, DMF). Trials on different conditions were performed and a final recommendation was provided to ZHP Chuannan. The project report did not address the formation of impurities or the change of the impurity profile itself.

D2. [Major] (ex Def. n. 3) - As part of the root cause analysis of the NDMA/NDEA contamination, the development of the 2011/2012 revised valsartan manufacturing process (introduction of the ZnCl₂ process) was reviewed and the following observations were made:

- a. The modified process was developed by the Huahai Pharmaceuticals R&D facility 'Shanghai SynCores Technologies Inc.'. Contrary to what the company stated in their retrospective analysis of the process change, the core principles of ICH Q8, Q9 and Q10 were not considered and potential impurity profiles and associated risks were not addressed by the R&D laboratory;



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MINISTERIO
DE SANIDAD, CONSUMO
Y BIENESTAR SOCIAL

- b. Furthermore, no risk assessment was made by the company to identify the impurities related to the new solvent used (DMF) when implementing the process proposed by R&D.

EU GMP Part II no. 2.21, 12.11; ICH Q9, ICH Q10 no. 3.2, ICH Q11 no. 3.1.4

Company's response:

Risk management was updated to consider the core principles of the ICH guidelines, referencing also to R&D relevant activities. The new procedure "Outsourcing Management for New Drug Substance" (SOP RD-009-1) was drafted.

Inspectors' comments: answer not sufficient. The company did not provide evidence that they have planned to assess if similar flaws exist also for other products' process developments. During the next inspection the team will verify the approach outlined in the CAPA by selecting appropriate examples.

Further documents related to the introduction of the $ZnCl_2$ process were reviewed:

- Valsartan development report ($ZnCl_2$) 2008-2012
- Valsartan Impurity Profile Analysis Report: Dated 10 April 2012, drafted by technical department of Chuannan site (East)
- Change Request for $ZnCl_2$ process implementation: requested 19/05/2011, effective 15/06/2011

The '2008-2012 development report' was a retrospective comparative analysis after the $ZnCl_2$ process implementation. It comprised the comparison of analytical data of the TEA and $ZnCl_2$ processes. It should be noted that the company committed to follow ICH Q8, Q9, Q11 requirements in the context of the implementation the $ZnCl_2$ process.

The change control documentation reflected the origin of the process change (i.e. the reasons, such as low yield, were mentioned). The change was categorized as critical. The appendix 1, section 7 (Change description of Valsartan process II, $ZnCl_2$ – process) addressed the safety and potential impurities, but failed to address potential side reactions and/or by-products due to the different solvents, reactants and reaction conditions (see deficiency D2.b - Major).

One major goal of the inspection was to verify/evaluate the sequence of measures the firm executed/put in place after the NDMA contamination became known. The firm declared to have received the first information about potential contamination on 22nd May 2018 via a complaint sent from Novartis (n. CC-18004) related to the presence of an unknown peak in 16 batches of Valsartan¹. In a first investigation (report QCC-18005 v.1) the unknown peak was misidentified as dichloromethane (range 20-78 ppm) even if the result was unsubstantiated.

The peak was identified on 6th June by the laboratory Solvias (appointed by Novartis to perform the study) as possibly NDMA, using a GC-MS method. As per the complaints files, the in-house investigation by ZHP was not initiated until June 6th, following this second communication by Novartis.

Complaint records are kept in an Excel spreadsheet. Compliance to EU GMP Annex 11 of spreadsheets was not verified during the inspection. Separate complaint logs are kept for East and West site; the capability to detect problems' recurrence for issues that affect both sites was not reviewed.

The following deficiency was observed:

D3. [Major] (ex Def. n. 4) - The company's approach to handling complaints was considered insufficient. The inspection team concluded that the company's actions after they received information indicating quality-related problems did not employ a structured approach to identify the root cause(s). Furthermore, it was

¹ C5355-18-014M, 027M, 032M, 034M, 035M, 036M, 037M, 038M, 039M, 040M, 041M, 042M, 043M, 044M, 045M and 046M.

Mod. 372/02 – GMP Inspection report	Rev. 0	Date: 8/10/2015	Page 9 of 33
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GOBIERNO DE ESPAÑA

MINISTERIO DE SANIDAD, CONSUMO Y BIENESTAR SOCIAL

considered that the efforts, formalities, and documentation of the investigations reviewed were inadequate for the potential level of risk and not in line with ICH Q9. The lack of understanding that a sound system for handling complaints is essential for process improvement, product and process understanding and the eventual quality of the active pharmaceutical ingredients manufactured, contributed to the late detection of NDMA and therefore delayed the implementation of the necessary regulatory actions. Also, some gaps were identified in the chain of events and therefore, in general, they cast doubts on the validity of the chain of events shown to the inspectors. This was evidenced by the following observations:

- a. The system does not record all notifications from customers that deserve investigation as being related to a quality issue; some of the complaints are re-defined as inquiries. During the inspection it was seen that the company had already started investigating the issue of unknown peaks in GC-FID chromatograms from December 2017/January 2018. However, there are no records of a complaint until 22 May. Some additional details may be found in the body of the inspection report;
- b. The inspection team reviewed the documentation for complaint CC-18004, received on 22 May 2018 from customer Novartis (Ireland) - unknown peak detected on 16 batches of valsartan:
 - i. The provided "typical chromatogram" of valsartan (GC, residual solvents) used to identify the unknown peaks and to provide an answer to Novartis's complaint was not related to any of the batches concerned by the complaint, but was related to complaint investigations requested by Sun Pharmaceuticals in November 2016;
 - ii. After being asked why no direct comparison of the unknown peaks observed by Novartis and their own GC chromatograms had been made, the company stated that they were not in possession of the customer's method at the time of the complaint. However, after a review of GC audit trails it became evident that the company had already obtained the Novartis method in December 2017. From further checks on the communications between the company and Novartis it became evident that Novartis had shared their GC-FID method with Z. Huahai already in July 2017, as a means of supporting investigations on unknown peaks;
 - iii. Although mentioned in the response sent via email to Novartis, there was no evidence that the investigation report had been attached to the communication;
 - iv. The inspection team checked the raw data for one batch concerned by the complaint (C5533-18-046M): a discrepancy was observed between the Open Lab audit trail - which showed no modification- and the pdf-audit trail of the raw data (stored at: <http://192.168.65.1/ecm/Enterprise.asp?SessID=182054>), which showed that a modification had been made on 26 May 2018 at 12:18:26. The comment "Integral the unknown peak for Novartis" was reported in the pdf audit trail;
- c. Novartis's complaint documentation (CC-18004) included a GC-MS chromatogram for valsartan batch C55-18-053M. The batch was released on 27 February 2018. On 12 March, i.e. 13 days after the batch was released, additional investigations with regard to a non-integrated peak with an approximate retention time of 6.8 or 6.9 were conducted. This investigation led to a GS-MS analysis of the batch. However, there was no GMP (or any other) documentation available covering these investigations. Furthermore, the potential impact on the quality of an already released batch was not discussed;
- d. Some additional observations were made with regard to the investigation reports associated with complaint investigation CC-18004:
 - i. There was no reference to the batches included in the complaint: the initial complaint listed 16 batches and 12 more batches were included afterwards, but the complaint records did not include any information about the affected batches. The batches were listed in the associated investigation only;

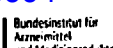


- ii. Records were incomplete: relevant communications to/from the customers were not included in the file. E.g. notification about additional batches was missing and responses sent to Novartis were not part of the documentation;
- iii. Checks performed as part of the complaint investigation were either not applicable or irrelevant, and the company could not provide information about the actions taken: e.g. it was reported that checks of training/compliance with a "current procedure" (which was not identified) were made, or that relevant batch records had been verified but without referring to any specific batch record numbers. This in general casts doubts on the accuracy of the records;
- iv. The document did not include a reference to the complaint;
- e. The following observations were made with regard to the email communication that the company received from Sun Pharmaceutical Industries Ltd, Mumbai, on 17 November 2016 (see point b.i. above in this deviation). The email informed Zhejiang Huahai about an interference regarding the toluene retention time, some unknown peaks and the presence of peaks due to methanol and ethanol, considered suspicious as these solvents were not part of the manufacturing process. Although the query was related to potential quality problems (N.B.: NDMA retention time is near toluene), it was not treated according to GMP, i.e. as a customer complaint. Furthermore, the documentation provided in this context showed that Sun Pharmaceuticals had already informed Zhejiang Huahai about unknown peaks and the toluene retention time inference on 16 October 2014.

EU GMP Part II no. 2.32.11, no. 15.11, 15.12; ICH Q9, ICH Q10 no. 3.2.1, 3.2.4, 4.1

Company's response:

- **Point a:**
 - The company repeated the date and time of what they considered to be the first information about unknown peaks in Valsartan API: "At 00:00 (China standard time (GMT+8)) on 22 May 2018, the email from Novartis with regard to the issue of unknown peaks in residual solvent method was received by Huahai for the first time." and stressed that the previous email/document exchange with Sun Pharma about unknown peaks was only a "technical communication"
 - Company revised customer complaints procedure
 - The procedure was strengthened to specify that "all complaint/quality event information from customers should be registered in corresponding form"
- **Point b:**
 - QA dept. has performed an investigation about the management of the complaint CC-18004. The timeline of e-mail correspondence between Novartis has been summarized by QA.
 - In the complaint document of CC-18004, when Huahai QA printed the email of Huahai's response to Novartis, the printing manner was incorrect (only the main body of the email was captured and printed), which led to the consequence that the attachment in the email cannot be visually identified in the printed document
 - what is described in this observation [point b(iv)] was caused by the design of the Agilent software, which is according to the company, clearly not a data integrity issue
 - As for the discrepancy observed between the Open Lab audit trail, the firm have consulted with Agilent technical support team, the design of audit trail of Agilent software contributed to the discrepancy, "where audit trail and log in the software is classified by each module function, and the audit trial of each section is relatively independent." Therefore there is discrepancy between the Open Lab audit trail and the pdf-audit trail of the raw data. In Annex 4b-3 of the CAPA plan is attached a statement issued by Agilent Technologies.
 - SMP-011.08 has been revised by QA, it is required in Section 5.5 that the original record of customer complaint (i.e. email between customer and Huahai) should be printed, and the email should be printed in a way that the attachment can be visually identified.



- It was only found out later by Huahai that the results from the GC-FID investigation could be used to address the questions about unknown peaks raised in Novartis's complaint of 22 May 2018
- **Point c:** with regard to the statement of "However, there was no GMP (or any other) documentation available covering these investigations. Furthermore, the potential impact on the quality of an already released batch was not discussed": the company stated that because this GC-MS investigation was conducted as part of the continuous investigation per Sun Pharma's request, which was classified as technical communication/inquiry, it was not treated as Customer Complaint.
- **Points d.i. and d.ii:** root Cause: when QA collected original complaint records (emails with customers), not all relevant e-mails and information were included in the complaint documentation due to carelessness of QA. Personnel was retrained
- **Points d.iii. and d.iv:** the Check List items performed as part of the complaint investigation were not specific; hence, "SMP-017.06 The deviation investigation management procedures" has been revised by QA to add the following requirement in Section 6.4.4 to address this issue
- **Point e:** Due to the same reason that the original communication between Ranbaxy (and then Sun Pharma) and Huahai was categorized as a technical communication/exchange/inquiry, it was not treated as Customer Complaint.

Inspectors' comments:

As a general comment, from the description of the content of complaint management related SOPs in the CAPA and the response received, it is noted that the company seems to have misunderstood that the inspection team did not question the adequacy of the quality documents, but their actual execution in the context of the Valsartan NDMA contamination incident.

- **Point a:** answer not satisfactory.
 - The definition of a "customer quality event" is not clear and therefore led to the masking of an actual customer complaint, although QA oversight is now included in the SOP. The SOP states that *"After communication, there is difference and disagreement between two parties regarding quality specification, analytical method, testing results and chromatograms, which might need further technical confirmation and study"*. For instance, topics like specifications and analytical methods are expected to be mutually agreed within a contractual quality agreement and therefore not supposed to be subject to a "quality event".
 - Furthermore, it seems that by repeating the date and time of the receipt of the Novartis complaint that the company did not understand that the inspectors obtained evidence that investigations on unknown peaks started way earlier (cf Sun Pharma email exchange, thread with last reply by ZHP on 11 May 2018, 12H02) and that those were not adequately treated in the Company's QMS in order to identify and mitigate any risk towards the patients. See inspectors' comments in section 4c
- **Point b.i:** answer incomplete. No documented evidence was provided to support the statement *"It was only found out later by Huahai that the results from the GC-FID investigation could be used to address the questions about unknown peaks raised in Novartis's complaint of 22 May 2018"*. In addition this information about the utilization of an old "typical chromatogram" was not explained to the complainant.
- **Point b.ii:** answer incomplete. Even in the case the answer given during the inspection was based on misunderstanding or translation errors, the firm did not provide an answer to the inspector's original question as to why no comparison of the unknown peaks observed by Novartis and their own GC chromatograms was made.
- **Point b.iii:** answer not sound. The company did not provide evidence regarding which settings were disabled leading to the non-show of an email attachment. Furthermore, the header of the email attached (and signed manually) to the complaint document documentation did not show any



Chinese characters. Therefore, no evidence could be provided that Novartis received the investigation report via the email sent on 31 May 2018 at 20:38.

- **Point b.iv:** the correct batch number 'C5523-18-046M' was noted. The validity of the company's justification will be verified during the next inspection.
- **Point c:** answer not satisfactory. The inspectors clarified already during the inspection that the nature and extent of the investigations triggered by Sun Pharmaceuticals cannot be regarded as 'technical communication' because it was related to the quality of the API as evidenced by the recall of medicines worldwide due to the contamination issue. However, aside from the terminology and the reason of specific investigations, the company did not implement one of the basic GMP requirements which is to ensure that any deviation, OOS or other information which indicates potential quality problems with the associated batches needs to be investigated in order to ensure that patients are not at risk.
- **Points d.i. to d.iv:** answer noted. The handling of complaints will be verified during the next inspection.
- **Point e:** answer not satisfactory. See inspectors comment to point c.

After the contamination was recorded in the company's QA system in 2018, the company executed investigations and risk assessments, which were evaluated during the inspection. The following observations were raised:

D4. [Major] (ex Def. n. 1) - The investigations conducted in the context of the NDMA/NDEA contamination of valsartan, and the related risk assessments, showed significant flaws, as indicated by the following observations:

- In the root cause analysis of the contamination of valsartan produced by the $ZnCl_2$ process, DC_E – 18001, only one root cause (process-related) was considered; the risk analysis/root cause investigation did not systematically consider all potential contributing factors. Some potential root causes (such as the quality of the water used during the synthesis – potable water, which could be a potential source of nitrate/nitrite contamination, recovered solvents and raw materials) were not evaluated, neither the impact on the intermediates manufactured in each workshop (N.B.: in workshop 12 also early Valsartan intermediates, both for internal use and for sale, are manufactured). For instance, the potable water used throughout the manufacturing process and its content of nitrate/nitrite had not been regularly tested. In addition, the potential impact or the contribution of potable water to the overall content of nitrate/nitrite in the reaction mass after tetrazole ring formation was not considered. Moreover, residual chlorine is routinely tested in potable water, with the specification "NLT 0.05 mg/L", but its potential risk was not evaluated;
- There was no risk assessment of other reagents and solvents with regard to the presence of nitrite/nitrate;
- Stage 2 intermediate is a secondary amine, controlled during the stage 3 manufacturing step via an in-process control with a limit of NMT 2.0%. The fate of this impurity was not addressed although it presents a possible risk upon further reaction in stage 4 (cycloaddition reaction with sodium azide) resulting in a secondary amine which is susceptible to nitrosation (i.e. introduction of a nitroso group). The risk assessment does not consider potential nitroso by-products;
- Risk assessment DC_E – 18003 (related to the TEA process and NDMA/NDEA contamination) did not contain enough detail to be able to evaluate the proposed root causes: e.g. while it contained a list of the recovered solvents used during the process, no critical assessment of their potential contribution to the contamination had been performed, taking into consideration, for example, the process stage where they are used, the difference in boiling points between recovered



GOBIERNO DE ESPAÑA

MINISTERIO DE SANIDAD, CONSUMO Y BIENESTAR SOCIAL

solvents and NDMA/NDEA, etc. With regard to the risk of cross-contamination due to potential inefficient cleaning of the equipment used for both the TEA and ZnCl_2 processes, no assessment had been made about the effectiveness of cleaning procedures, production in campaign mode or duration of the campaigns. Only general statements were provided in the document;

- e. The hypotheses proposed on the potential root causes had not been verified or checked against existing data from real contaminated batches. Laboratory scale experiments to confirm the proposed root causes had not been considered;
- f. In workshop 4, where the risk of cross-contamination due to shared equipment or residual solvents had been ruled out because only the TEA process was performed in this workshop, the most probable root cause identified was the potential contamination of raw materials (e.g. TEA) with secondary amines, in theory attributable to cross-contamination incidents at the supplier's facility: no further investigation to confirm this hypothesis had been conducted so far because, according to what the company declared during the inspection, the priority of this investigation was reduced following the change in the manufacturing process;
- g. The risk assessments did not include the evaluation of the potential impact of the TEA impurity profile on the NDEA level in losartan potassium and candesartan cilexetil (TEA is still used in the manufacturing process of these APIs) or the identification of risk-mitigating measures;
- h. In the risk assessment of other APIs manufactured in the facility - RARC-20180827 version 01 (east zone) and RARD-20180827 version 01 (west zone):
 - i. There was no specific assessment on the shared workshops 6 for the east zone and W05 for the west zone, where sartan and non-sartan products are manufactured;
 - ii. The document did not mention all the intermediates manufactured in workshop 6.

EU GMP Part II no. 2.2; ICH Q9

Company's response:

The company completed corrective actions for points a, b, e, g, h

The updated deviation investigation was provided (DCE-18003 version 2).

- Point a: new investigation was conducted also according to revised Risk management Procedure SMP-023. Risk assessment was implemented including investigation on additional root cause and tests of secondary amines, nitrite, NDMA, NDEA, DMA, DEA in raw materials, recovered solvents, potable water and intermediates. Risk control measures were proposed based on the risk evaluation and test results. Some lab scale studies on the old process and some spike studies were conducted
- Point b: presence of nitrite/nitrate was evaluated in other reagents and solvents
- Point c: risk assessment did not consider potential nitroso by-products – appendix 1c. Action pending (target date: 30 Nov 2018)
- Point d: more details were included in the updated version of DCE-18003. Target date: 30 Nov 2018. Cleaning procedures were updated and now a change-over cleaning is required also when switching between different processes of the same product
- Point e: tests on batches and lab scale experiments simulating the old processes were conducted.
- Point f: further investigation to confirm the hypothesis of potential contamination of raw material TEA with secondary amines was conducted. DEA was detected (section 4.5.5 - therefore risk of forming NDEA), but not DMA (therefore no risk of forming NDMA). Additionally, the following pending actions have been planned: on-site audits have been scheduled and specifications of TEA HCl, TEA and DMF will include limits for DMA and DEA



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MINISTERIO DE SANIDAD, CONSUMO Y BIENESTAR SOCIAL

- **Point g:** the risk assessments were performed
- **Point h:** Risk assessment for APIs and intermediates manufactured in workshops 6 and W05 was completed.

The company concluded that:

- The TEA process and original ZnCl_2 process are obsolete
- Control of NDMA in the optimized process is obtained via a process design change (separate azide quenching, performed not in the presence of the product)
- Enhanced control of raw materials was implemented, revising the following specifications: DMF (to include limit for DMA), potable water (nitrite content to be tested monthly), recovered toluene and ethyl acetate from step 4 (test for NDMA).

Inspectors' comments:

Most of these items are related to the control strategy to be described in the CEP application, and to be approved by assessors. The responses and the actions proposed by the company in the CAPA will be reviewed as part of the on-going evaluation of the revisions of the relevant CEP applications submitted by the company to EDQM.

Additionally, the following items will be checked during next inspection:

- Actions still pending
- The revised specifications of materials and results from testing will be reviewed on site in order to verify their effective implementation

With regards to the other sartans manufactured at the site, the risk assessment report RARC-20180904 version 01 (nitrosamine impurities in Huahai's sartans) and report RARC-20180824 version 01 (covering only NDMA in sartans) were provided.

Losartan potassium:

- CEP 2009-296 Losartan potassium (designated as process II): tetrazole ring already present in starting material BBTT. DMF is used in the starting material synthesis. In addition, the risk of NDMA presence is low since no nitrite is used during the synthesis of BBTT and two further process steps are performed by the company after BBTT introduction into the process
- CEP 2010-139 Losartan potassium: TEA used in tetrazole formation step (last step of the synthesis) and sodium-nitrite is used for azide quenching, therefore this process bears a potential risk of NDEA formation

Losartan potassium is made in the east zone, in workshops 1, 3, 6 and 7:

- Losartan potassium CEP 2010-139 (process II, designated as Bromo OTBN process) is manufactured in workshops 1 and 7
- Losartan potassium CEP 2009-296 (BBTT process) is manufactured in workshops 3
- Intermediate trityl losartan is made in workshop 6 and intermediate losartan base is manufactured in workshops 1 and 7

Irbesartan is manufactured in the east zone, in workshops 4, 10 and 17. The manufacturing process, as declared by the company, foresees usage of TEA but sodium nitrite is not used. Therefore, the risk for nitrosamine formation would seem to be unlikely.

Mod. 372/02 – GMP Inspection report	Rev. 0	Date: 8/10/2015	Page 15 of 33
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GOBIERNO DE ESPAÑA

MINISTERIO DE SANIDAD, CONSUMO Y BIENESTAR SOCIAL

The inspection team reviewed relevant documents supporting the revised 2018 process implementation aimed to remove risks of NDMA formation, mainly by disconnecting the NaN_3 quenching step from product containing phases. In the optimized process there is no "azide" quenching with sodium nitrite in the presence of Valsartan; Toluene is introduced instead of MTBE (Methyl tert-butyl ether) to improve phase separation (step 4):

- Process change triggered by Change request: PCRC-18022 (east site only), initiated on 12 July 2018,
- Impurity Profile Analysis Report, dated 12 July 2018, (IPO)
- Product Development Report, Product Lifecycle summary, approved 23 August 2018
- Process Validation Protocol/Report, crude Valsartan, (C5523), PVC-18014 (P), PVC-18014 (R), Report approved 23 August 2018, Workshop 13

The Change Control documentation comprised a number of individual documents stating completion of the actions identified:

- Attachment B of Change Control form: Update sequence
 - 12/07/18: Engineering to adjust piping system (same day as Change Control initiation)
 - 16/07/18: Analytical R&D (Quality Research): Completed method validation for NDMA version 2
 - 23/07/18: Technical department completed process operation procedure, Master Batch Record template, finished product quality standard revision (specification) plus process validation protocol crude finalized plus training
 - 13/08/18: QC completed Stability Study protocol
 - 23/08/18: Technical department completed Process Validation report, signed off by QA (east site, WS 13 and west site WS 02)
 - 25/08/18: WS supplementary work
- Change Control Annex

The following documents were not part of the change control documentation PCRC-18022 (East site only), but part of the company's risk mitigation measures evaluation:

- 14/06/18 and 15/06/18 and 17/06/18: Laboratory trials, carried out by technical department east zone, e.g.
 - Test of solubility in DMF at lower temperatures
 - Washing solution/concentration
 - Laboratory trial on 17/06/18 discussed the removal of NaNO_2 (excess azide removed by washing only); NB: The trial was successful on lab level, but trial production failed (protocol approved 30/06/2018, conducted 07-12 July 2018, covered by Change Control PCRC-18019, initiated 27/06/18)
- 16/06/2018 and 23/06/18: Meeting about optimization of process, high level staff, QA people, technical and QC staff

In the context of the 2018 development of the revised process the following observations were raised:

D5. [Major] (ex Def. n. 2) - The company's risk assessment in the context of the development/implementation of the revised Valsartan process, conducted in July/August 2018, was considered inadequate, as evidenced by the following observations:

- a. The risks associated with the revised azide quenching step (which in the new optimised process is performed in the aqueous phase following phase separation, but not in the presence of the product) introduced a new significant risk of azide carry-over into the final active substance:
 - i. No formalised risk assessment was made to determine the potential risks specifically introduced by the change in the process;

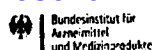


- ii. The potential carry-over of the mutagenic impurity "azide" in the final API was not discussed as such. Furthermore, no test strategy was laid down in order to determine the reduction of azide content, i.e. to confirm by testing that the washing steps were effective:
 - Solvents or mother liquors were not tested;
 - No challenge spike tests were performed;
 - Crude valsartan was not tested for azide content.
- iii. No justified control strategy was developed to ensure efficient removal of azide;
- b. The company failed to develop and implement a justified control strategy to identify the temperatures of the reaction mass during phase separation, which is performed between 70 and 90 °C, as a critical process parameter. The company believed that this broad temperature range does not constitute a critical process parameter; however, they acknowledged that the temperature is essential in order to achieve effective phase separation;
- c. The revised valsartan manufacturing process allows solvent recovery, but this has not been properly implemented:
 - i. The change control concerning the change in the manufacturing process does not include the impact on recovered solvents or the need to validate the recovery process;
 - ii. The SOPs and the specifications do not address the issue of recovered solvents from the new process and need to be updated/revised (e.g. Specs. QS-S606.08 Quality Standard of Valsartan recovered solvents, effective date 13 January 2018);
 - iii. The recovery of solvents from the new process has not been validated;
- d. The following observations with regard to the development of the optimised process after NDMA detection in July/August 2018 were made:
 - i. Although initial considerations/discussions about NDMA risk mitigation (e.g. process changes) started on 18 June 2018, no documents on risk assessment and mitigation measures were part of the formal change control documentation initiated on 12 July 2018. This could lead to an insufficient assessment during the implementation of the proposed change. Furthermore, it was noticed that activities supposed to be discussed/implemented within the change control procedure had already been carried out before the change was initiated;
 - ii. Equipment changes were made simultaneously with the initiation of change control; some of the equipment changes were not considered as GMP relevant because they dealt with the separation/treatment of used solvents inside of GMP facilities.

EU GMP Part II no. 2.21, 12.11, 13.12; ICH Q9; ICH Q11, no. 6

Company's response:

- Point a: The Risk assessment related to the change of process was updated to cover analysis of the new potential risks introduced with the revised process. Additionally, the company declared to have conducted spike studies to demonstrate azide removal/purging capability of the process; results are reported in Annex 2 of RARD-20181106, version 01. The firm concluded that *"Although the amount of azide residue is low under the optimized process conditions, the residual risk is still increased compared with the original process, so the azide residue is added in the specifications of crude valsartan and valsartan drug substance with the limit of not more than 4.7 ppm (based on TTC)."*



GOBIERNO DE ESPAÑA

MINISTERIO DE SANIDAD, CONSUMO Y BIENESTAR SOCIAL

- Point b: temperature is now defined as a critical parameter. Master batch record will be updated accordingly (deadline: 31 December 2018). Point c: solvent recovery process will be validated (deadline: 30 March 2019). Point d: risk assessment RARD-201 81106 version 01 performed.

Inspectors' comments: answer noted. The following points will be further discussed during next inspection:

- point a - with regard to updated Valsartan specification, Appendix 1a-3 (specification of crude valsartan) does not include a specification for azide content, which is only included in the specifications of the final API. This discrepancy between what stated in the CAPA plan and what reported in the updated specifications will be clarified in the context of the evaluation of the revision application submitted to EDQM, and as needed checked during next inspection;
- point bii: it was not clarified how to prevent future activities to be implemented prior to the opening of a change.
- Also, the progress/completion of the actions still pending will be verified.

During the inspection the company showed to the inspector a draft version of the revised Change control procedure SMP-018.05: the draft introduces section 5.19 (API process change), requiring a full scan by GC-MS for residual solvents of product in case it was necessary to compare the impurity data before and after the change.

D6. [Other] (ex Def. n. 11) - The following observations were made with regard to the change control procedure SMP-018.05:

- a. The SOP requires a risk assessment to be performed but it does not cross-refer to the risk assessment procedure;
- b. It does not explicitly require an assessment of cross-contamination risks and there is no reference to the cross-contamination procedure;
- c. It does not require an evaluation of the toxicity of new introduced molecules, potency, allergenicity, etc., major expansion of buildings and facilities, introduction of new products in the facility or introduction of a different process for same product, impurity profiles of new products to be manufactured, etc. The company has a procedure which deals with some of these aspects SOP (SOP CB-1731-1) but this is not referenced in the change control procedure.

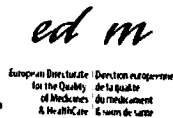
EU GMP Part II no. 2.21; ICH Q9; ICH Q10: 3.2.3, 4.1

Company's response:

The change control procedure was revised (SMP-018.07): a cross reference to the risk assessment procedure was included; requirements to evaluate risk of cross-contamination, toxicity, potential impurities etc. of new molecules in the context of a change were added.

Inspectors' comments: answer acceptable. The correct application of the revised procedure will be checked during next inspection.

New specification for Valsartan was implemented with regard to nitrosamine issue; the limit for NDMA (NMT 0.3 ppm) was included. The process water specification was not changed. The limits for NDMA (NMT 0.3 ppm) were implemented in the specification of recovered toluene (step 4) and recovered ethyl acetate (from steps 4 and 5).



D7. [Other] (ex Def.n. 14) - Following the NDMA incident, the company issued SOP TE-007-1 (Mutagenic impurity identification and control management system. Approval date 22 August 2018. Effective date: 30 September 2018). It will be applicable to both ZHP Chuannan and ZHP Xunqiao sites and it is an implementation of ICH M7 in the company's quality system. As required by ICH M7, it will apply to new APIs and post-approval changes; however, taking into consideration the NDMA/NDEA contamination issue and considering that during the inspection many gaps were identified in the company's approach to manufacturing process development, it is the inspection team's opinion that the CAPA plan should also include an assessment of the other APIs manufactured on site.

EU GMP Part II no. 2.21; ICH Q9

Company's response:

The evaluation was started for both Chuannan and Xunqiao sites. Expected completion date: 31 December 2018. Priority was given to the five high risk sartans (Candesartan, Valsartan, Irbesartan, Losartan potassium and Olmesartan). The company declared to have sent these reports to EDQM for their evaluation and that risk control measures have been put in place.

Inspectors' comments: this will be reviewed as part of the on-going evaluation of the revisions of the relevant CEP applications submitted by the company.

Personnel

According to the firm's Site Master File, in August 2018 about 2042 staff was employed by the company with the following distribution: QA: 63, QC: 122, production and technical: 1415, storage and distribution 67, engineering: 124, and 251 in other departments.

The inspection did not cover any GMP requirement related to personnel.

Buildings and facilities / Process Equipment

Valsartan was manufactured both in the East and West zone.

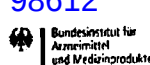
The firm declared that Valsartan was manufactured in the East Zone in the following locations: workshop 2 and 4 (building no. 08), workshop 12 (building no. 13, dismantled and under renovation) and workshop 13 (building no.14). In the West zone it was manufactured in workshop WS02 (building no. 58).

Each workshop has a dedicated solvent recovery facility, used to recover solvents used for all the processes performed in the workshop.

During the inspection it was communicated by the firm that Valsartan is manufactured in dedicated workshops, that solvents recovery facilities are workshop-dedicated and that solvents cannot be used for different productions.

The inspectors verified that the workshops which the company declared to be used for Valsartan production were dedicated and therefore this would exclude the risk of cross-contamination with other productions and the risk of contamination with NDMA and NDEA from Valsartan to other APIs.

The manufacturing facilities inspected in the context of the scope of the inspection were considered as fit for their intended purpose. Cleaning and maintenance seemed appropriately applied. However, due to the limited areas seen, no general statement on the GMP compliance of the production facilities can be given.

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With regard to potential risk of cross-contamination between different Valsartan processes and between Valsartan and its intermediates, it was found that:

- With the exception of workshop 4 (East Zone, building no. 03, where only TEA process was performed), in the other workshops listed above both the TEA and $ZnCl_2$ processes were carried out, with the consequent risk of cross-contamination between the two processes (therefore potential presence of NDMA in batches manufactured with the TEA process and potential presence of NDEA in batches manufactured using the $ZnCl_2$ process). Being NDMA and NDEA unexpected impurities, the firm had not considered them during the cleaning validation studies.
- Additionally, as reported in deficiency n. D4.a, in workshop 12 Valsartan was manufactured together with early Valsartan intermediates, two of which can be sold (they are listed in Annex 3). As these intermediates are manufactured in the same workshop and also solvents recovery facility is in common with late stages of Valsartan production, the risk that NDMA/NDEA contamination could be found also in these early intermediates due to cross-contamination cannot be excluded.

Production

One of the main objectives of the inspection was to review the process development as well as the commercialization of the products in order to understand if failures in development of control strategies, establishment of critical quality attributes, critical process parameters (CPP) as well as validation contributed to the NDMA/NDEA contamination of Valsartan. Therefore, the team reviewed a number of related documents as well as the validation protocol of the revised process aimed to mitigate the risk of contaminations. Deficiencies D2 and D5 (both Major, described in the "Quality Management" section of this report) were observed.

Documentation and records

The inspection was not intended to review thoroughly the firm documentation system. However, various types of documents including paper-based and electronic documentation were checked.

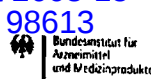
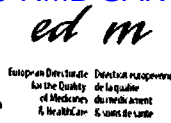
D8. [Other] (ex Def. n. 10) - References/Coding of the deviations do not allow for proper tracking/trending: the numbering system is not consistent for all deviations as it allows, "when necessary", a sub-letter to also be included; each time a new letter is added, the numbering restarts from scratch. This makes it difficult to track deviations and evaluate re-occurrences.

EU GMP Part II no. 2.32.4, 6.10

Company's response:

Deviation Investigation Management System procedure was revised (SMP-017.07) to redefine the numbering system of deviation; sub-letters representing different departments will no longer be used for numbering of deviations.

Inspectors' comments: answer acceptable. Correct application will be checked during next inspection. Also the numbering system of other quality related documents will be evaluated.



Material Management / Storage and distribution

Considering the inspection's scope, the firm's approach on materials management and/or storage/distribution was only checked in order to determine potential risks of contamination/cross contamination by Valsartan or Valsartan intermediates by incorrect handling and/or warehousing of the respective materials.

The correct segregation and quarantining of batches known to contain contaminants, and the correct handling of returned batches, were also reviewed. Due to the high volume of batches affected, several warehouses were allocated for the storage of quarantined/rejected Valsartan batches. Storage areas are located on several floors of buildings 16 and 78-west. These warehouses are identified as quarantine areas in their entirety. The company relies on segregation and identification of drums; there is no IT-based system for materials management.

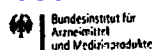
Blending and reprocessing

According to the company procedures it is not possible to blend batches manufactured in different workshops and no blending of products with different codes is foreseen (therefore in theory batches of Valsartan obtained using the TEA and $ZnCl_2$ process could not be blended).

This practice could not be verified during the inspection, as evidenced in the following deficiency:

D9. [Major] (ex Def. n. 7) - One of the key aspects which had to be evaluated during the inspection was the firms' approach to blending and reprocessing/reworking, especially with regard to the contamination of batches manufactured with the old TEA process in workshop 4, which was dedicated to this process and therefore not at risk of cross-contamination with the new process. As detailed below in the deviation, a severe lack of traceability was observed on this matter and during the inspection it was not possible to verify if batches obtained with the old and the new process had been reprocessed and/or blended. Therefore, the team concluded that GMP failures in reprocessing could be one of the potential primary root causes of the contamination of batches manufactured using the old TEA process, at least in the TEA-process-dedicated workshop 4. The company failed to provide to the inspection team the requested documentation in order to verify the issue and exclude this possibility, evidenced as follow:

- a. A SOP (SMP-025.03) specifies that for APIs close to the retest date it is possible to perform the drying process step in order to assign a new manufacturing date and therefore a new retest date. This is considered inappropriate as the drying step would not be able to remove potential degradation products and it could not be used to extend the retest date;
- b. The SOP states that this option can also be used to put unreacted material back into the process. The company was therefore requested to provide examples of when this is performed and what control measures are in place but they confirmed this option is not implemented in any production and it was included only because it is mentioned in ICH Q7. The option should be removed from the SOP as it is not applicable to the operations performed by the company;
- c. The SOP stipulates that batches close to their retest date could be blended, but it is not clear how this would allow an old batch to be used for further production. According to what is correctly stated in the blending procedure, the blended batch would be assigned the retest date of the oldest batch. The company is requested to clarify the rationale and provide relevant examples;
- d. During the inspection it was not possible to trace which batches had been reprocessed in order to extend the retest date and what manufacturing steps had been carried out. Also, the company was not able to provide evidence that these reprocessed batches are reported as such in the Annual Product Review. The few documents presented by the company were obviously not



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complete: according to the company, these batches could be traced via the forms filled by warehouse personnel during their periodic checks on batches close to the retest date. The company was requested to provide all the forms filled in during the past 5 years, but only 10 forms were provided (3 for the east zone and 7 for the west zone, in both cases all referred only to the year 2018). Additionally, from the numbering of the forms, it was clear that for the west zone at least 26 forms had been filled in but only 7 were shown to the inspectors and no additional information was later provided; all of them were related to intermediates or APIs used for pilot scale studies.

EU GMP Part II no. 8.44, 14.20, 6.15

Company's response:

Reprocess and Rework Management Procedure was revised (SMP-025.04) as follows:

- If reprocessing is performed by drying step no new manufacturing date can be assigned to extend the retest date of the batch (point a of the deficiency)
- The option related to unreacted material back into the process was eliminated (point b of the deficiency)
- A Material Reprocessing/Reworking log has been added for tracing these operations. The procedure also states that reprocessed/reworked batches will be included in Annual Product Reviews (point d of the deficiency)

Regulation on product expiry/retest date was revised (SMP-030.05) as follows:

- Eliminated the possibility of blending batches close to their retest date. The firm declared that, after reviewing historical data, they could verify that this option was never used (point c of the deficiency)
- Batches close to their expiry/retest date should be evaluated according to the Quality Risk Management Procedure. More details were added to describe management of these batches. The procedure also states that during annual product review QA is required to review the disposition of products close to expiry/retest date (point d of the deficiency)

Inspectors' comments: answer not complete. The traceability of the reprocessed batches as requested during the inspection was not provided. Traceability/correct application of the revised procedures will need to be verified during next inspection.

Process Validation

The team checked the validation documentation of the revised Valsartan process, August 2018. The firm validated a batch size of 690-806 kg in the West zone and of 348-407 kg in the East zone.

The Process Validation Protocol/Report, crude Valsartan (C5523) PVC-18014 (P), PVC-18014 (R), Report approved 23 August 2018 and related to workshop 13 was reviewed. The validation was to be conducted in July/August. The protocol, approved on 12 July 2018 covered in its scope the:

- Validation of crude Valsartan manufacturing step
- Stability studies for APIs



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- The protocol makes reference to a risk assessment that was carried out in the context of the change control handling: Annex 2, section 5, risk assessment, covered the following aspects: Main process impurity evaluation, including genotoxic impurities (NaN₃, NDMA)

Cleaning

Cleaning procedures and records in the Valsartan dedicated workshops were reviewed.

SOP for cleaning (SOP DB-1096-5) and the cleaning frequency were revised. The logbook of reactor W02-203-1 was examined to check the records of the cleaning operations.

The SOP for cleaning established different levels of cleaning:

- Simple: performed for example if cleaning holding time is overdue and after maintenance. This cleaning is carried-out loading water plus NaOH through the manhole. Rinsing is repeated until neutral pH is obtained. Insufficient instructions are provided
- Changeover: it applies also in case different products codes of the same API are manufactured in the same workshop
- Routine: at the end of the campaign, cleaning needs to be performed within 24 hours after finishing the campaign, or if production is expected to start again after more than 5 days. It consists of partial equipment dismantling and rinsing twice with water and NaOH. Records of verifications are just a Y/N; there are no instructions of how to proceed

The following deficiencies were observed:

D10. [Other] (ex Def. n. 17) - The SOP for cleaning of reactors (SOP DB-1096-5) did not provide enough detail on the checks required to verify the cleaning process. It did not contain instructions on the critical points to check or on the use of ancillary tools in order to verify critical parts (e.g. flashlight or mirror). Cross-contamination points could therefore remain unnoticed.

EU GMP Part II no. 5.21

Company's response:

The "Cleaning Procedure of Reactor (W02-203-1/2/3) for Valsartan (D5191) Crude post" was revised (SOP DB-1096-6), adding the section "Visual inspection method and acceptance criteria".

Inspectors' comments: answer acceptable.

D11. [Other] (ex Def. n. 12) - Cross-contamination control is managed via the procedure "Sanitization management in the manufacturing area", SOP PR-015-1. The following observations were made:

- There is no specific procedure with a holistic approach to the issue; all data and risk assessments are scattered and refer for example to cleaning validation, equipment etc., but there is no higher level of control which considers all criticalities together in the light of cross-contamination;
- There is no requirement for cross-contamination risk assessment, to be repeated periodically based on products' hazard level (toxicity), review of design and flow of materials, personnel, equipment (also mobile equipment), reconfiguration of lines, training of personnel, case by case evaluation of gowning needs, cleaning SOPs, etc.;
- There is no reference to the risk assessment SOP in the procedure;

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- d. The risk assessment for the multipurpose workshop W05, RARD-170701 version 01, 6 August 2017, describes the manufactured products, the HVAC system, the equipment etc. but it does not address specifically the cross-contamination risk in order to verify if the procedures in place, the equipment and the flows are designed in order to minimise the risk of cross-contamination.

EU GMP Part II no. 2.21; ICH Q9

Company's response:

The new procedure Preventing Management Procedure of Drug Contamination & Cross-contamination (SOP PR-016-1) was drafted in order to cover points a, b, c, d of the deficiency.

The risk assessment related to workshop W05 (RARD-20181026 version 01) was updated to cover evaluation of cross-contamination risk.

Inspectors' comments: answer acceptable.

NDMA/NDEA Analytical methods validation

The Analytical methods used for NDMA/NDEA in Valsartan, Losartan potassium, Irbesartan, Olmesartan medoxomil and Candesartan cilexetil were evaluated during the inspection.

Valsartan

- Validation data QRC-18027 (R) of GC-MS method for NDMA (LOD: 0.1 ppm; LOQ: 0.25 ppm)
- Validation data QRC-18053 (R) of GC-MS method for NDEA (LOD: 0.025 ppm; LOQ: 0.05 ppm)

Losartan-Potassium

- Validation data QRC-18052 (R) of GC-MS method for NDMA (LOD: 0.1 ppm; LOQ: 0.25 ppm)
- Validation data QRC-18051 (R) of GC-MS method for NDEA (LOD: 0.025 ppm; LOQ: 0.05 ppm)

Irbesartan

- Validation data QRC-18054 (R) of GC-MS method for NDMA (LOD: 0.1 ppm; LOQ: 0.25 ppm)
- Validation data QRC-18055 (R) of GC-MS method for NDEA (LOD: 0.041 ppm; LOQ: 0.082 ppm)

Olmesartan medoxomil

- Validation data QRC-18088 (R) of GC-MS method for NDMA (LOD: 0.1 ppm; LOQ: 0.25 ppm)
- Validation data QRC-18089 (R) of GC-MS method for NDEA (LOD: 0.172 ppm; LOQ: 0.344 ppm)

Candesartan cilexetil

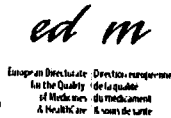
- Validation data QRC-18059 (R) of LC-UV method for NDMA (LOD: 0.1 ppm; LOQ: 0.25 ppm)
- Validation data QRC-18058 (R) of LC-UV method for NDEA (LOD: 0.13 ppm; LOQ: 0.25 ppm)

Quality Control laboratory

The team did not perform a general inspection of the entire QC facilities related to the testing of APIs, but focused on isolated QC aspects that were in relation to the scope of the inspection.

The following deficiencies were observed:

Mod. 372/02 – GMP Inspection report	Rev. 0	Date: 8/10/2015	Page 24 of 33
-------------------------------------	--------	-----------------	---------------



D12. [Major] (ex Def. n. 8) - During the review of the GC-FID analytical test it was observed that the filing system does not allow identification and retrieval of primary analytical data for a given batch. Electronic data are not stored and organised in a manner that this could be performed without checking paper-based certificates of analysis. Thus, the identification of repeated analyses for one batch in the system is impossible.

EU GMP Part II no. 6.60, Annex 11: 7.1

Company's response:

The company performed an investigation and found that when dealing with a large number of batches, that are analyzed in a given sequence or in sequential sequences, the use of the search function to retrieve primary analytical data for these batches in GC-FID system would be less efficient. Nevertheless, when it comes to retrieval of primary analytical data for a single given batch in GC-FID system, the search function of the software would be more effective. The firm updated the SOP "Recording and Review Procedure for Laboratory" (SOP QC-021-12).

Inspectors' comments: Answer ambiguous. The firm referred to different sections of the SOP. The highlighted sections 5.7 to 5.7.1.2 in appendix 8-2 don't address the observations. The compliance of the actual implementation will be checked during the next inspection.

D13. [Major] (ex Def. n. 9) - The evaluation performed by the company in relation to the presence of unknown peaks in GC-MS valsartan sample chromatograms was insufficient. For instance, the company did not characterise peaks appearing after the NDMA peak in the new optimised valsartan process (batches D5191-18-233, D5191-18-234, D5191-18-235, D5191-18-236, D5191-18-237). This should have been included in the company's risk assessment in order to minimise the risk of other potential genotoxic impurities being present.

EU GMP Part II no. 2.21, 2.32.4; ICH Q11 3.1.4

Company's response:

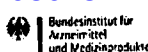
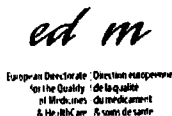
Investigation MVD-18091(R) version 01 was performed. The company stated that the peak had not been labelled because previously a full scan mode GC-MS method was used, not sensitive enough to detect this low intensity peak. The recently validated method uses the mode of single ion detection (of the molecular ion of NDMA), which is more sensitive: the identity of the peak at approximately 10.6 min was confirmed with this new method as methyl valerate (not genotoxic impurity), via a retention time match between spiked methyl valerate and the unknown peak.

The NDMA analytical method of Valsartan by GC-MS was revised:

- a table with the relative retention times of 4 peaks (toluene, n-butyl acetate, methyl valerate, DMF) was included in the procedure
- the updated method states that a deviation investigation should be initiated if the peak area of any future unknown peak in the chromatogram of the sample solution is bigger than the peak area of NDMA in the chromatogram of the standard solution.

The firm stated that also the NDMA/NDEA methods for the other sartans will be revised to include the requirement on deviations investigations of unknown peaks (target date: 30 Dec 2018)

Mod. 372/02 – GMP Inspection report	Rev. 0	Date: 8/10/2015	Page 25 of 33
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GOBIERNO DE ESPAÑA

MINISTERIO DE SANIDAD, CONSUMO Y BIENESTAR SOCIAL

Inspectors' comments: answer only partially acceptable.

- The identity of methyl valerate has to be better justified. When the work is completed, the specification of Valsartan should be updated accordingly (if relevant) and the new method as well as full validation data and chromatograms should be submitted to EDQM via a request for revision of the CEP application. The same applies to the other sartans as necessary.
- The company did not provide information on the calculation of the recovery rate of methyl valerate which would also have provided further information on the ratio (AUC) between the concentration of the impurity in the batch analysed and the overall concentration of the spiked solution. Moreover, the sample ID in Fig 4 and 5 (sample ID: D5191-18-242) differs from the one mentioned in section 3 of the "Investigation of the Unknown RT10.6 min Impurity in GC-MS method for valsartan NDMA test" (batch No. D5191-18-225)
- With regard to the general approach to management and investigations of future unknown peaks, the rationale for considering only peaks which are bigger than the area of the one for NDMA is not scientifically justified. This should be reconsidered, taking into account the ratio signal/noise and peaks from the blank solutions. A suitable approach should be designed not only for sartans but for all APIs manufactured at the site

The completion of the CAPA and the new approach will be verified on practical examples during next inspection.

D14. [Other] (ex Def. n. 16) - During inspection of the QC laboratory it was observed that sample management does not ensure proper identification and traceability of incoming samples:

- a. The reference given to each sample does not allow it to be identified unequivocally; the same code (batch number only) is used for several samples. A unique number exists (CoA number), but this is not used to identify the samples;
- b. A properly designed "sample reception log" does not exist: the currently used logbook lists received samples but also requests for analysis without incoming samples: in the latter case, the test will be performed using the remainder of a previous sample received weeks or even months before. For example, for batch C5562-18-009 a sample was received on 8 July 2018 (CoA 4088), and another entry in the registry was made on September 10 (CoA 4794) in order to run other analysis on the same sample; batches C5523-18-410 and C5523-18-411: samples received on 31 July 2018, and another entry was made on Aug 17 (without an actual sample). In all the examples, there was no cross-reference between the first and the second entries in order to locate the correct sample;
- c. The format of the sample logbook allows for changes in the data and re-creation of entries, e.g. regarding the date of reception or the person who received the sample.

EU GMP Part II no. 6.60

Company's response:

An investigation was performed, procedure and format of sample receipt logbooks have been revised to ensure a more clear traceability of the different requests of analysis (registration form Q/ZHH QC-043 for analyses on incoming samples against one or multiple specifications; registration form Q/ZHH QC-369 for analyses to be performed on samples already in QC form previous analyses, re-calculations and/or reporting of results according to specific customers' requirements etc.)

Mod. 372/02 – GMP Inspection report	Rev. 0	Date: 8/10/2015	Page 26 of 33
-------------------------------------	--------	-----------------	---------------



Inspectors' comments: answer acceptable. The correct application will be verified during next inspection.

D15. [Major] (ex Def. n. 5) - In order to verify the general approach to OOS management, the inspection team reviewed OOS investigations related to a single unknown impurity of crude pregabalin. OOS-DQC 18004, recorded on 17 January 2018, referred to substantial out-of-specification results of batches D2526-18-015 and D2526-18-017. Two days later, on 19 January, two more OOSs for the same test were detected for batches D2526-18-020 and D2526-18-21 and recorded as OOS-DQC 18005. The following observations were made with regard to OOS/Deviations handling:

- a. The company did not open separate OOS investigations to trace different out-of-specification results for different batches. This approach does not consider that the root causes could be different for each batch even if they were all tested within the same run of the same analysis. The combination of several out-of-spec batches into a single OOS was considered as not in compliance with GMP. Furthermore, with this approach the system cannot keep track of the total number of OOSs identified;
- b. During the investigation, after further testing, it was discovered that the initial batches suspected to be out-of-specification were within specification but that 3 other batches were out-of-specification instead (batches D2526-18-14, -16, -19), showing high values of a single unknown impurity. No new OOSs for these additional out-of-spec batches were opened;
- c. The OOS investigations did not try to identify why the company failed to detect the actual out-of-spec batches during the regular QC analysis;
- d. The inspection team checked the batch records of the crude pregabalin batches in question and noticed that for batch D2526-18-018, the supervisor of the operator that conducted the manufacturing operations, who was supposed to verify the correct performance of the centrifugation step, had signed the relevant section in the batch record the day before the centrifugation operations were carried out (manufacture date: 15 January 2018, check: 14 January 2018). Furthermore, the incident had not been noticed and/or discussed in the context of the OOS investigations;
- e. The company identified human error as the root cause: the operator(s) did not open a valve to allow water to wash the centrifuge cake and had left the valve to the source reactor open. Therefore, no washing of the cake took place. As a result of the root cause investigations, it was concluded that the operator was a new employee that was not well trained. However, it was not discussed how the supervisor could have overlooked the actual wrong positions of the valves.

EU GMP Part II no. 2.32-4, 11.15

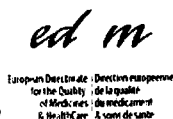
Company's response:

Point a: OOS/OOT Investigation Management Procedure has been revised to improve the numbering principles: 1) For the same batch, OOS/OOT result caused by different testing items, number shall be assigned separately. 2) When an OOS/OOT event occurs in the same experiment or in the same analysis sequence, one OOS number will be opened initially for Phase I investigation to assess if there was a laboratory error. If no laboratory error is identified a separate OOS/OOT number will be assigned for each of the involved batches.

Point b: in order to further improve the system, SMP-021.10 OOS/OOT Investigation Management Procedure has been revised to improve the numbering principles.

Point c: The run time for each injection by the HPLC method for crude Pregabalin is 37 min, while the concerned impurity eluted at 66.7min (37+29.7=66.7min). Therefore, it cannot be detected during current injection of the HPLC analysis of crude Pregabalin of that particular batch; however it can be eluted and

Mod. 372/02 – GMP Inspection report	Rev. 0	Date: 8/10/2015	Page 27 of 33
-------------------------------------	--------	-----------------	---------------

GOBIERNO
DE ESPAÑAMINISTERIO
DE SANIDAD, CONSUMO
Y BIENESTAR SOCIAL

detected at the injection that immediately followed. ... To overcome this problem, we will implement a CAPA to add a blank injection at the end of each sequence.

Point d: No CAPA provided

Point e: On page 5 of the investigation report (OOS-DQC18004), the description of Section 5

"Operators" has discussed the reasons why the supervisor did not notice the wrong position of the valves: because the valves of drinking water for washing were installed outside the centrifuge room, when the supervisor confirmed that the valves for drinking water were closed and returned to centrifuge room, the washing operation had ended.

Inspectors' comments:

Point a: Answer acceptable.

Point b: Answer noted. The inspection team stresses the fact that the OOS system deployed at the time of the inspection did not allow to keep track of all OOS occurred. Given the size of the company and the large number of products, it cannot be expected that all individual OOS files were needed to be opened in order to count manually the batches involved in OOS events. Furthermore, this approach doesn't allow – as required by GMP- the analysis of trend in order to detect potential systematic failures in production and quality control.

Point c: Answer noted. The firm's approach of allowing the carry-over of impurities of a previous injection to the next sample run because of an incomplete elution of the column will be checked during the next inspection.

Point d: Answer not satisfactory. The company's reply was restricted to root cause analysis. No corrective and preventative actions were provided.

Point e: Answer not satisfactory. The location of the valves was known to the supervisor; therefore the provided root cause is considered as not sound.

During the inspection also OOS-CQC18030, batch n. C20213-18-115 (intermediate of valsartan step 2) was reviewed: a result of 0.6% was found for an impurity normally detected via HPLC at RT 27.753 in this intermediate (but not in the final API). Specification: $\leq 0.5\%$.

In July 2018 this impurity was identified with LC-MS method, showing the presence of an alerting structure; the acceptable limit should be 4.7 ppm. The current HPLC related substances method has a LOD of 200 ppm, not sufficient to routinely detect such a low level.

The CAPA proposed by the company was to reprocess the intermediate with a deadline for reprocessing before 31 December 2018. LC-MS will be performed: deadline 30 Jan 2019.

The company is planning to add a control for this specific impurity in the new process.

Two batches of the API obtained with the new process were tested, this impurity was below 4,7 ppm.

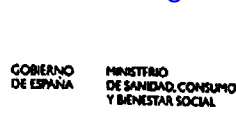
The Critical Process Parameters with potential impact on this impurity have not been identified yet, additional studies are currently ongoing.

Sampling

The inspection team sampled in total 10 batches of Valsartan APIs. Different criteria in the selection were taken into account. The samples have been analysed for the presence of NDMA by the Official Medicines Control Laboratories of Ireland and the United Kingdom.

The test reports are attached to this report, **Annex 4**.

The company is requested to comment on the high result of batch c5271-17-288 (96.6ppm), whereas the firm's own test resulted in not detected.



Recovery and re-use of materials

Apart from solvents, no recovery of other materials (including mother liquor) is performed for Valsartan. The procedure allows for the recovery of methanol, ethyl acetate from several stages (condensation, crude Valsartan and final crystallization). Fresh ethyl acetate only is used for the final purification step. The SOP for solvent recovery in workshop W02 was revised. In some steps (e.g. crystallization step), solvent recovery includes a neutralization step and phase separation.

Specifications for solvents are defined in QS-S606.8 (Quality standard of valsartan recovered solvents, effective date 13 Jan 2018).

With regard to the use of recovered solvents as potential source of nitrosamine contamination, refer to deficiency D4.a (Major) and D5.c and D5.d.ii (Major).

Particularly relevant is D5.c - Major (described already above in this report, section "Quality Management") regarding flaws in the implementation of solvents recovery in the context of the 2018 revised Valsartan manufacturing process because:

- The change control concerning the change in the manufacturing process does not include the impact on recovered solvents or the need to validate the recovery process
- The SOPs and the specifications do not address the issue of recovered solvents from the new process and need to be updated/revised (e.g. Specs. QS-S606.08 Quality Standard of Valsartan recovered solvents, effective date 13 January 2018)
- The recovery of solvents from the new process has not been validated

Recalls

Recalls are managed via procedure SMP-013.07, which is correctly designed. The following deficiency was identified:

D16. [Major] (ex Def. n. 6) - No recall was formally initiated to manage the actions related to the contaminated batches. The company had sent notifications to customers outside the Quality Management System, and thus failed to comply with GMP requirements. The company declared that they were still collecting feedback but during the inspection it was verified that, as the actions had been managed outside of the recall procedure, no measures had been taken to guarantee that all customers had been contacted and that a reconciliation of the batches shipped had been performed.

EU GMP Part II no. 2.12, 2.15, 2.16, 2.30, 15.12

Company's response:

The recall procedure already included APIs manufactured by ZHP in its scope, nevertheless the firm revised it to include more details (SMP-013.08). With regard to the specific issue raised during the inspections, a recall protocol for Valsartan from foreign market was approved on 15 September 2018. The recall was initiated and expected to be completed by 31 December 2018.

Inspectors' comments: answer not acceptable. According to the Valsartan recall protocol, the company decided to start a "recall" of the batches of Valsartan which were still within their retest date (*"To ensure all the Valsartan API batches within retest period in customers' warehouse can be returned to Huahai, it is planned to conduct recall"*). This might mean that the firm would start a recall only in case batches needed to be returned, therefore failing to fully understand the concept of "recall". Also, the recall was classified as "Grade 2", which according to the recall procedure is assigned when *"the drug might induce temporary or reversible harms to health"*. This classification is not justifiable as "Grade 1", assigned when *"the drug might induce serious harms to health"*, would seem to be more appropriate in case of impurities that have

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mutagenic and genotoxic effects as both processes are evidently not reversible. These points will need to be clarified during next inspection.

Another procedure is also available with regard to incidents managements. It was observed that:

D17. [Other] (ex Def. n. 13) - SOP QA-002-1 Product quality incident management regulation, Section 5.2.7, states that serious quality incidents should be communicated in a timely manner to authorities and clients, both inside and outside China. During the inspection it was confirmed that only the customers were notified (and through them the communication reached the various regulatory competent authorities). The company holds one CEP for valsartan and is involved as a manufacturer in several others, but the communication was not sent to EDQM.

EU GMP Part II no. 15.15

Company's response:

Product quality incident management regulation was revised (SOP QA-002-2) to specify that in case of serious quality incidents it is necessary to inform foreign regulatory authorities; for products covered by CEPs the company will inform directly EDQM.

Inspectors' comments: answer acceptable

Contract manufacturing (including laboratories)

See D2 - Major, described in the section "Quality Management" of this report.

Comparison between registration documents and manufacturing process

In the light of the upcoming process change, the verification of regulatory filings (i.e. CEP dossier) was not performed.

Site Master File

During the preparation phase of the inspection, the firm submitted a SMF [C-SMF-41, approved 18 August 2018]. However, the document was not subject to review.

Miscellaneous

Nothing to report

Attachments

Annex 1: list of the deficiencies, sent to the company via email on 18 October 2018

Annex 2: products manufactured at ZHP XunQiao site

Annex 3: products manufactured at ZHP Chuannan site

Annex 4: NDMA test reports OMCLs



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Summary and conclusions

ZHP XunQiao site

On the basis of the information the firm provided during the spot-checks carried out at the following site and after reviewing the answers and commitments provided in reply to the initial report, the opinion of the inspection team is that the company:

ZHEJIANG HUAHAI PHARMACEUTICAL CO., LTD.
XunQiao, Linhai,
Zhejiang 317024, China

Taking into account that:

- Valsartan API is not manufactured at this site
- no materials are in common between the Chuannan and XunQiao sites
- the risk assessments performed by the company

it can be concluded that there is a low risk of potential cross-contamination derived from Valsartan and the APIs manufactured at this site. Unless new information/events indicate otherwise, a follow-up inspection/evaluation at this site would not be considered to be a priority.

ZHP Chuannan site

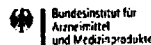
On the basis of the deficiencies observed during the for-cause inspection of the company and after reviewing the answers and commitments provided in reply to the list of deficiencies, the opinion of the inspection team is that the company:

ZHEJIANG HUAHAI PHARMACEUTICAL CO., LTD.
Chuannan, Duqiao, Linhai
Zhejiang 317016, China

could not provide sound evidence that all the deficiencies observed were addressed adequately and therefore a new inspection is considered necessary to verify the implementation of the corrective and preventative action plan put in place and to check if the deficiencies that were not properly addressed have been rectified.

As already described in the body of this report, the information provided by the firm during the inspection seem also to indicate that there is no potential risk of cross-contamination between Valsartan and other APIs. Nevertheless, during the inspection a potential risk of cross-contamination which could occur between Valsartan and the early Valsartan intermediates manufactured in workshop 12 was identified.

In addition to the CAPA assessment performed by the inspection team, the corrective actions proposed with regard to process developments and/or changes will be verified also during the next inspection by selecting suitable APIs. It is recommended that also a follow-up of the studies on-going at the time of the inspection (i.e.: additional control for the specific impurity detected in the new process, as identified during investigation of OOS-CQC18030 – see chapter “Quality control laboratory” in this report) is performed.



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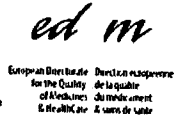
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The firm's comments on the NDMA test results obtained by the Official Medicines Control Laboratories of Ireland and the United Kingdom which were requested on the 20 November 2018 could not be part of the CAPA submission and therefore could not be assessed in the context of the issuance of this final inspection report. Nevertheless the Company is requested to submit them within four weeks after receiving this final inspection report.

This inspection report does not indemnify the company against non-observed deficiencies.

Signatures

Name and organisation	Function	Date	Signature
Ms Cristina BACCARELLI; ITALIAN MEDICINES AGENCY, AIFA, ITALY	Lead inspector	12 Dec 2018	
Dr Thomas HECKER; EDQM, COUNCIL OF EUROPE	Inspector	12 Dec 2018	
Dr Manuel IBARRA LORENTE; AGENCIA ESPAÑOLA DE MEDICAMENTOS Y PRODUCTOS SANITARIOS, AEMPS, SPAIN	Inspector	12 Dec 2018	
Dr Igor POPOVIC; EDQM, COUNCIL OF EUROPE	Expert	12 Dec 2018	
Dr Corina NACHTSHEIM; FEDERAL INSTITUTE FOR DRUGS AND MEDICAL DEVICES, BfArM, GERMANY	Expert	12 Dec 2018	



GOBIERNO DE ESPAÑA

MINISTERIO DE SANIDAD, CONSUMO Y BIENESTAR SOCIAL

Definition of Significant Deficiencies

1 Critical Deficiency

A deficiency which has produced, or leads to a significant risk of producing either a product which is harmful to the human or veterinary patient or a product which could result in a harmful residue in a food producing animal.

2 Major Deficiency

A non-critical deficiency:

which has produced or may produce a product, which does not comply with its marketing authorisation;

or

which indicates a major deviation from EU Good Manufacturing Practice;

or

(within EU) which indicates a major deviation from the terms of the manufacturing authorisation;

or

which indicates a failure to carry out satisfactory procedures for release of batches or (within EU) a failure of the Qualified Person to fulfil his legal duties;

or

a combination of several "other" deficiencies, none of which on their own may be major, but which may together represent a major deficiency and should be explained and reported as such.

3. Other Deficiency

A deficiency, which cannot be classified as either critical or major, but which indicates a departure from good manufacturing practice.

(A deficiency may be "other" either because it is judged as minor, or because there is insufficient information to classify it as a major or critical).



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LIST OF DEFICIENCIES

Joint inspection between EMA (AIFA/AEMPS) and EDQM (in the context of the Inspection Programme of manufacturers within the Certification Procedure)

Inspected site:

ZHEJIANG HUAHAI PHARMACEUTICAL CO., LTD.

Chuannan, Duqiao, Linhai

Zhejiang 317016, China

Spot-checks at:

ZHEJIANG HUAHAI PHARMACEUTICAL CO., LTD.

Xunqiao, Linhai,

Zhejiang 317024, China

References:

EDQM: INSP 2018-039-P01

EMA: INS/GMP/2018/070 and INS/GMP/2018/071

Lead Inspector	Ms Cristina BACCARELLI	ITALIAN MEDICINES AGENCY, AIFA, ITALY
Inspector	Dr Thomas HECKER	EDQM, COUNCIL OF EUROPE
Inspector	Dr Manuel IBARRA LORENTE	AGENCIA ESPAÑOLA DE MEDICAMENTOS Y PRODUCTOS SANITARIOS, AEMPS, SPAIN
Expert	Dr Igor POPOVIC	EDQM, COUNCIL OF EUROPE
Expert	Dr Corina NACHTSHEIM	FEDERAL INSTITUTE FOR DRUGS AND MEDICAL DEVICES, BfArM, GERMANY

Inspection date: 10 – 13 September 2018

N.B.: the inspection was mainly carried out at the **Chuannan site**, where Valsartan is produced. It is to be noted that some of the procedures-related deviations refer also to the **Xunqiao site** because many of the procedures are applicable to both sites.

- Deviations applicable to both sites: dev. "Major" 7 (points a, b, c) and deviations "Other" n. 10, 11, 12, 13, 14
- One deviation is specifically referred to the Xunqiao site, as clearly indicated in the deviation itself (dev. 15, Other)

The company is kindly requested to specify in the CAPA plan which corrective/preventative actions are applicable also to the Xunqiao site, also in case deviations other than the ones listed above should be relevant for both sites.

Note: at the end of this document the "Definition of Significant Deficiencies" (according to the "Compilation of Community Procedures on Inspections and Exchange of Information") is provided.

Please also note that during the inspection there were a number of issues observed which are aspects related to both the content of the CEP dossiers and GMP. You should therefore ensure that the information relative to these issues is submitted in both your response to the inspection findings and in each of the concerned CEP applications, as already requested to you by EDQM (CEP_RZ_PH_2010-072-1137692, dated 4 October 2018).

List of Deficiencies (9 classified as “Major” and 8 classified as “Other”)

MAJOR

1. The investigations conducted in the context of the NDMA/NDEA contamination of valsartan, and the related risk assessments, showed significant flaws, as indicated by the following observations:
 - a. In the root cause analysis of the contamination of valsartan produced by the ZnCl_2 process, DC_E – 18001, only one root cause (process-related) was considered; the risk analysis/root cause investigation did not systematically consider all potential contributing factors. Some potential root causes (such as the quality of the water used during the synthesis – potable water, which could be a potential source of nitrate/nitrite contamination, recovered solvents and raw materials) were not evaluated, neither the impact on the intermediates manufactured in each workshop (N.B.: in workshop 12 also early Valsartan intermediates, both for internal use and for sale, are manufactured). For instance, the potable water used throughout the manufacturing process and its content of nitrate/nitrite had not been regularly tested. In addition, the potential impact or the contribution of potable water to the overall content of nitrate/nitrite in the reaction mass after tetrazole ring formation was not considered. Moreover, residual chlorine is routinely tested in potable water, with the specification “NLT 0.05 mg/L”, but its potential risk was not evaluated;
 - b. There was no risk assessment of other reagents and solvents with regard to the presence of nitrite/nitrate;
 - c. Stage 2 intermediate is a secondary amine, controlled during the stage 3 manufacturing step via an in-process control with a limit of NMT 2.0%. The fate of this impurity was not addressed although it presents a possible risk upon further reaction in stage 4 (cycloaddition reaction with sodium azide) resulting in a secondary amine which is susceptible to nitrosation (i.e. introduction of a nitroso group). The risk assessment does not consider potential nitroso by-products;
 - d. Risk assessment DC_E – 18003 (related to the TEA process and NDMA/NDEA contamination) did not contain enough detail to be able to evaluate the proposed root causes: e.g. while it contained a list of the recovered solvents used during the process, no critical assessment of their potential contribution to the contamination had been performed, taking into consideration, for example, the process stage where they are used, the difference in boiling points between recovered solvents and NDMA/NDEA, etc. With regard to the risk of cross-contamination due to potential inefficient cleaning of the equipment used for both the TEA and ZnCl_2 processes, no assessment had been made about the effectiveness of cleaning procedures, production in campaign mode or duration of the campaigns. Only general statements were provided in the document;
 - e. The hypotheses proposed on the potential root causes had not been verified or checked against existing data from real contaminated batches. Laboratory scale experiments to confirm the proposed root causes had not been considered;

- f. In workshop 4, where the risk of cross-contamination due to shared equipment or residual solvents had been ruled out because only the TEA process was performed in this workshop, the most probable root cause identified was the potential contamination of raw materials (e.g. TEA) with secondary amines, in theory attributable to cross-contamination incidents at the supplier's facility: no further investigation to confirm this hypothesis had been conducted so far because, according to what the company declared during the inspection, the priority of this investigation was reduced following the change in the manufacturing process;
 - g. The risk assessments did not include the evaluation of the potential impact of the TEA impurity profile on the NDEA level in losartan potassium and candesartan cilexetil (TEA is still used in the manufacturing process of these APIs) or the identification of risk-mitigating measures;
 - h. In the risk assessment of other APIs manufactured in the facility - RARC-20180827 version 01 (east zone) and RARD-20180827 version 01 (west zone):
 - i. There was no specific assessment on the shared workshops 6 for the east zone and W05 for the west zone, where sartan and non-sartan products are manufactured;
 - ii. The document did not mention all the intermediates manufactured in workshop 6.
2. The company's risk assessment in the context of the development/implementation of the revised valsartan process, conducted in July/August 2018, was considered inadequate, as evidenced by the following observations:
 - a. The risks associated with the revised azide quenching step (which in the new optimised process is performed in the aqueous phase following phase separation, but not in the presence of the product) introduced a new significant risk of azide carry-over into the final active substance:
 - i. No formalised risk assessment was made to determine the potential risks specifically introduced by the change in the process;
 - ii. The potential carry-over of the mutagenic impurity "azide" in the final API was not discussed as such. Furthermore, no test strategy was laid down in order to determine the reduction of azide content, i.e. to confirm by testing that the washing steps were effective:
 - Solvents or mother liquors were not tested;
 - No challenge spike tests were performed;
 - Crude valsartan was not tested for azide content.
 - iii. No justified control strategy was developed to ensure efficient removal of azide;
 - b. The company failed to develop and implement a justified control strategy to identify the temperatures of the reaction mass during phase separation, which is performed between 70 and 90 °C, as a critical process parameter. The company believed that this broad temperature range does not constitute a critical process parameter; however, they acknowledged that the temperature is essential in order to achieve effective phase separation;
 - c. The revised valsartan manufacturing process allows solvent recovery, but this has not been properly implemented:
 - i. The change control concerning the change in the manufacturing process does not include the impact on recovered solvents or the need to validate the recovery process;
 - ii. The SOPs and the specifications do not address the issue of recovered solvents from the new process and need to be updated/revised (e.g. Specs. QS-S606.08 Quality Standard of Valsartan recovered solvents, effective date 13 January 2018);
 - iii. The recovery of solvents from the new process has not been validated;
 - d. The following observations with regard to the development of the optimised process after NDMA detection in July/August 2018 were made:

- i. Although initial considerations/discussions about NDMA risk mitigation (e.g. process changes) started on 18 June 2018, no documents on risk assessment and mitigation measures were part of the formal change control documentation initiated on 12 July 2018. This could lead to an insufficient assessment during the implementation of the proposed change. Furthermore, it was noticed that activities supposed to be discussed/implemented within the change control procedure had already been carried out before the change was initiated;
 - ii. Equipment changes were made simultaneously with the initiation of change control; some of the equipment changes were not considered as GMP relevant because they dealt with the separation/treatment of used solvents inside of GMP facilities.
3. As part of the root cause analysis of the NDMA/NDEA contamination, the development of the 2011/2012 revised valsartan manufacturing process (introduction of the ZnCl_2 process) was reviewed and the following observations were made:
 - a. The modified process was developed by the Huahai Pharmaceuticals R&D facility 'Shanghai SynCores Technologies Inc.'. Contrary to what the company stated in their retrospective analysis of the process change, the core principles of ICH Q8, Q9 and Q10 were not considered and potential impurity profiles and associated risks were not addressed by the R&D laboratory;
 - b. Furthermore, no risk assessment was made by the company to identify the impurities related to the new solvent used (DMF) when implementing the process proposed by R&D.
4. The company's approach to handling complaints was considered insufficient. The inspection team concluded that the company's actions after they received information indicating quality-related problems did not employ a structured approach to identify the root cause(s). Furthermore, it was considered that the efforts, formalities, and documentation of the investigations reviewed were inadequate for the potential level of risk and not in line with ICH Q9. The lack of understanding that a sound system for handling complaints is essential for process improvement, product and process understanding and the eventual quality of the active pharmaceutical ingredients manufactured, contributed to the late detection of NDMA and therefore delayed the implementation of the necessary regulatory actions. Also, some gaps were identified in the chain of events and therefore, in general, they cast doubts on the validity of the chain of events shown to the inspectors. This was evidenced by the following observations:
 - a. The system does not record all notifications from customers that deserve investigation as being related to a quality issue; some of the complaints are re-defined as inquiries. During the inspection it was seen that the company had already started investigating the issue of unknown peaks in GC-FID chromatograms from December 2017/January 2018. However, there are no records of a complaint until 22 May. Some additional details may be found in the body of the inspection report;
 - b. The inspection team reviewed the documentation for complaint CC-18004, received on 22 May 2018 from customer Novartis (Ireland) - unknown peak detected on 16 batches of valsartan:
 - i. The provided "typical chromatogram" of valsartan (GC, residual solvents) used to identify the unknown peaks and to provide an answer to Novartis's complaint was not related to any of the batches concerned by the complaint, but was related to complaint investigations requested by Sun Pharmaceuticals in November 2016;
 - ii. After being asked why no direct comparison of the unknown peaks observed by Novartis and their own GC chromatograms had been made, the company stated

- that they were not in possession of the customer's method at the time of the complaint. However, after a review of GC audit trails it became evident that the company had already obtained the Novartis method in December 2017. From further checks on the communications between the company and Novartis it became evident that Novartis had shared their GC-FID method with Z. Huahai already in July 2017, as a means of supporting investigations on unknown peaks;
- iii. Although mentioned in the response sent via email to Novartis, there was no evidence that the investigation report had been attached to the communication;
 - iv. The inspection team checked the raw data for one batch concerned by the complaint (C5533-18-046M): a discrepancy was observed between the Open Lab audit trail -which showed no modification- and the pdf-audit trail of the raw data (stored at: <http://192.168.65.1/ecm/Enterprise.asp?Session=182054>), which showed that a modification had been made on 26 May 2018 at 12:18:26. The comment "Integral the unknown peak for Novartis" was reported in the pdf audit trail;
- c. Novartis's complaint documentation (CC-18004) included a GC-MS chromatogram for valsartan batch C55-18-053M. The batch was released on 27 February 2018. On 12 March, i.e. 13 days after the batch was released, additional investigations with regard to a non-integrated peak with an approximate retention time of 6.8 or 6.9 were conducted. This investigation led to a GS-MS analysis of the batch. However, there was no GMP (or any other) documentation available covering these investigations. Furthermore, the potential impact on the quality of an already released batch was not discussed;
 - d. Some additional observations were made with regard to the investigation reports associated with complaint investigation CC-18004:
 - i. There was no reference to the batches included in the complaint: the initial complaint listed 16 batches and 12 more batches were included afterwards, but the complaint records did not include any information about the affected batches. The batches were listed in the associated investigation only;
 - ii. Records were incomplete: relevant communications to/from the customers were not included in the file. E.g. notification about additional batches was missing and responses sent to Novartis were not part of the documentation;
 - iii. Checks performed as part of the complaint investigation were either not applicable or irrelevant, and the company could not provide information about the actions taken: e.g. it was reported that checks of training/compliance with a "current procedure" (which was not identified) were made, or that relevant batch records had been verified but without referring to any specific batch record numbers. This in general casts doubts on the accuracy of the records;
 - iv. The document did not include a reference to the complaint;
 - e. The following observations were made with regard to the email communication that the company received from Sun Pharmaceutical Industries Ltd, Mumbai, on 17 November 2016 (see point b.i. above in this deviation). The email informed Zhejiang Huahai about an interference regarding the toluene retention time, some unknown peaks and the presence of peaks due to methanol and ethanol, considered suspicious as these solvents were not part of the manufacturing process. Although the query was related to potential quality problems (N.B.: NDMA retention time is near toluene), it was not treated according to GMP, i.e. as a customer complaint. Furthermore, the documentation provided in this context showed that Sun Pharmaceuticals had already informed Zhejiang Huahai about unknown peaks and the toluene retention time inference on 16 October 2014.
5. In order to verify the general approach to OOS management, the inspection team reviewed OOS investigations related to a single unknown impurity of crude pregabalin. OOS-DQC 18004, recorded

on 17 January 2018, referred to substantial out-of-specification results of batches D2526-18-015 and D2526-18-017. Two days later, on 19 January, two more OOSs for the same test were detected for batches D2526-18-020 and D2526-18-21 and recorded as OOS-DQC 18005. The following observations were made with regard to OOS/Deviations handling:

- a. The company did not open separate OOS investigations to trace different out-of-specification results for different batches. This approach does not consider that the root causes could be different for each batch even if they were all tested within the same run of the same analysis. The combination of several out-of-spec batches into a single OOS was considered as not in compliance with GMP. Furthermore, with this approach the system cannot keep track of the total number of OOSs identified;
 - b. During the investigation, after further testing, it was discovered that the initial batches suspected to be out-of-specification were within specification but that 3 other batches were out-of-specification instead (batches D2526-18-14, -16, -19), showing high values of a single unknown impurity. No new OOSs for these additional out-of-spec batches were opened;
 - c. The OOS investigations did not try to identify why the company failed to detect the actual out-of-spec batches during the regular QC analysis;
 - d. The inspection team checked the batch records of the crude pregabalin batches in question and noticed that for batch D2526-18-018, the supervisor of the operator that conducted the manufacturing operations, who was supposed to verify the correct performance of the centrifugation step, had signed the relevant section in the batch record the day before the centrifugation operations were carried out (manufacture date: 15 January 2018, check: 14 January 2018). Furthermore, the incident had not been noticed and/or discussed in the context of the OOS investigations;
 - e. The company identified human error as the root cause: the operator(s) did not open a valve to allow water to wash the centrifuge cake and had left the valve to the source reactor open. Therefore, no washing of the cake took place. As a result of the root cause investigations, it was concluded that the operator was a new employee that was not well trained. However, it was not discussed how the supervisor could have overlooked the actual wrong positions of the valves.
6. No recall was formally initiated to manage the actions related to the contaminated batches. The company had sent notifications to customers outside the Quality Management System, and thus failed to comply with GMP requirements. The company declared that they were still collecting feedback but during the inspection it was verified that, as the actions had been managed outside of the recall procedure, no measures had been taken to guarantee that all customers had been contacted and that a reconciliation of the batches shipped had been performed.
7. One of the key aspects which had to be evaluated during the inspection was the firms' approach to blending and reprocessing/reworking, especially with regard to the contamination of batches manufactured with the old TEA process in workshop 4, which was dedicated to this process and therefore not at risk of cross-contamination with the new process. As detailed below in the deviation, a severe lack of traceability was observed on this matter and during the inspection it was not possible to verify if batches obtained with the old and the new process had been reprocessed and/or blended. Therefore, the team concluded that GMP failures in reprocessing could be one of the potential primary root causes of the contamination of batches manufactured using the old TEA

process, at least in the TEA-process-dedicated workshop 4. The company failed to provide to the inspection team the requested documentation in order to verify the issue and exclude this possibility, evidenced as follow:

- a. A SOP (SMP-025.03) specifies that for APIs close to the retest date it is possible to perform the drying process step in order to assign a new manufacturing date and therefore a new retest date. This is considered inappropriate as the drying step would not be able to remove potential degradation products and it could not be used to extend the retest date;
 - b. The SOP states that this option can also be used to put unreacted material back into the process. The company was therefore requested to provide examples of when this is performed and what control measures are in place but they confirmed this option is not implemented in any production and it was included only because it is mentioned in ICH Q7. The option should be removed from the SOP as it is not applicable to the operations performed by the company;
 - c. The SOP stipulates that batches close to their retest date could be blended, but it is not clear how this would allow an old batch to be used for further production. According to what is correctly stated in the blending procedure, the blended batch would be assigned the retest date of the oldest batch. The company is requested to clarify the rationale and provide relevant examples;
 - d. During the inspection it was not possible to trace which batches had been reprocessed in order to extend the retest date and what manufacturing steps had been carried out. Also, the company was not able to provide evidence that these reprocessed batches are reported as such in the Annual Product Review. The few documents presented by the company were obviously not complete: according to the company, these batches could be traced via the forms filled by warehouse personnel during their periodic checks on batches close to the retest date. The company was requested to provide all the forms filled in during the past 5 years, but only 10 forms were provided (3 for the east zone and 7 for the west zone, in both cases all referred only to the year 2018). Additionally, from the numbering of the forms, it was clear that for the west zone at least 26 forms had been filled in but only 7 were shown to the inspectors and no additional information was later provided; all of them were related to intermediates or APIs used for pilot scale studies.
8. During the review of the GC-FID analytical test it was observed that the filing system does not allow identification and retrieval of primary analytical data for a given batch. Electronic data are not stored and organised in a manner that this could be performed without checking paper-based certificates of analysis. Thus, the identification of repeated analyses for one batch in the system is impossible.
9. The evaluation performed by the company in relation to the presence of unknown peaks in GC-MS valsartan sample chromatograms was insufficient. For instance, the company did not characterise peaks appearing after the NDMA peak in the new optimised valsartan process (batches D5191-18-233, D5191-18-234, D5191-18-235, D5191-18-236, D5191-18-237). This should have been included in the company's risk assessment in order to minimise the risk of other potential genotoxic impurities being present.

OTHER

10. References/Coding of the deviations do not allow for proper tracking/trending: the numbering system is not consistent for all deviations as it allows, "when necessary", a sub-letter to also be included; each time a new letter is added, the numbering restarts from scratch. This makes it difficult to track deviations and evaluate re-occurrences.
11. The following observations were made with regard to the change control procedure SMP-018.05:
 - a. The SOP requires a risk assessment to be performed but it does not cross-refer to the risk assessment procedure;
 - b. It does not explicitly require an assessment of cross-contamination risks and there is no reference to the cross-contamination procedure;
 - c. It does not require an evaluation of the toxicity of new introduced molecules, potency, allergenicity, etc., major expansion of buildings and facilities, introduction of new products in the facility or introduction of a different process for same product, impurity profiles of new products to be manufactured, etc. The company has a procedure which deals with some of these aspects SOP (SOP CB-1731-1) but this is not referenced in the change control procedure.
12. Cross-contamination control is managed via the procedure "Sanitization management in the manufacturing area", SOP PR-015-1. The following observations were made:
 - a. There is no specific procedure with a holistic approach to the issue; all data and risk assessments are scattered and refer for example to cleaning validation, equipment etc., but there is no higher level of control which considers all criticalities together in the light of cross-contamination;
 - b. There is no requirement for cross-contamination risk assessment, to be repeated periodically based on products' hazard level (toxicity), review of design and flow of materials, personnel, equipment (also mobile equipment), reconfiguration of lines, training of personnel, case by case evaluation of gowning needs, cleaning SOPs, etc.;
 - c. There is no reference to the risk assessment SOP in the procedure;
 - d. The risk assessment for the multipurpose workshop W05, RARD-170701 version 01, 6 August 2017, describes the manufactured products, the HVAC system, the equipment etc. but it does not address specifically the cross-contamination risk in order to verify if the procedures in place, the equipment and the flows are designed in order to minimise the risk of cross-contamination.
13. SOP QA-002-1 Product quality incident management regulation, Section 5.2.7, states that serious quality incidents should be communicated in a timely manner to authorities and clients, both inside and outside China. During the inspection it was confirmed that only the customers were notified (and through them the communication reached the various regulatory competent authorities). The company holds one CEP for valsartan and is involved as a manufacturer in several others, but the communication was not sent to EDQM.
14. Following the NDMA incident, the company issued SOP TE-007-1 (Mutagenic impurity identification and control management system. Approval date 22 August 2018. Effective date: 30 September

2018). It will be applicable to both the Z. Huahai Chuannan and Xunqiao sites and it is an implementation of ICH M7 in the company quality system. As required by ICH M7, it will apply to new APIs and post-approval changes; however, taking into consideration the NDMA/NDEA contamination issue and considering that during the inspection many gaps were identified in the company's approach to manufacturing process development, it is the inspection team's opinion that the CAPA plan should also include an assessment of the other APIs manufactured on site.

15. During the review of the risk assessment related to the products manufactured at the Xunqiao site (RARC-20180904) it was observed that it included only an assessment of the processes carried out at the site but it did not consider any other factors such as the quality of the potable water used during the synthetic step, potential contamination of the raw material TEA, etc.
16. During inspection of the QC laboratory it was observed that sample management does not ensure proper identification and traceability of incoming samples:
 - a. The reference given to each sample does not allow it to be identified unequivocally; the same code (batch number only) is used for several samples. A unique number exists (CoA number), but this is not used to identify the samples;
 - b. A properly designed "sample reception log" does not exist: the currently used logbook lists received samples but also requests for analysis without incoming samples: in the latter case, the test will be performed using the remainder of a previous sample received weeks or even months before. For example, for batch C5562-18-009 a sample was received on 8 July 2018 (CoA 4088), and another entry in the registry was made on September 10 (CoA 4794) in order to run other analysis on the same sample; batches C5523-18-410 and C5523-18-411: samples received on 31 July 2018, and another entry was made on Aug 17 (without an actual sample). In all the examples, there was no cross-reference between the first and the second entries in order to locate the correct sample;
 - c. The format of the sample logbook allows for changes in the data and re-creation of entries, e.g. regarding the date of reception or the person who received the sample.
17. The SOP for cleaning of reactors (SOP DB-1096-5) did not provide enough detail on the checks required to verify the cleaning process. It did not contain instructions on the critical points to check or on the use of ancillary tools in order to verify critical parts (e.g. flashlight or mirror). Cross-contamination points could therefore remain unnoticed.

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A deficiency which has produced, or leads to a significant risk of producing either a product which is harmful to the human or veterinary patient or a product which could result in a harmful residue in a food producing animal.

2 Major Deficiency

A non-critical deficiency:

which has produced or may produce a product, which does not comply with its marketing authorisation;

or

which indicates a major deviation from EU Good Manufacturing Practice;

or

(within EU) which indicates a major deviation from the terms of the manufacturing authorisation;

or

which indicates a failure to carry out satisfactory procedures for release of batches or (within EU) a failure of the Qualified Person to fulfil his legal duties;

or

a combination of several "other" deficiencies, none of which on their own may be major, but which may together represent a major deficiency and should be explained and reported as such.

3. Other Deficiency

A deficiency, which cannot be classified as either critical or major, but which indicates a departure from good manufacturing practice.

(A deficiency may be "other" either because it is judged as minor, or because there is insufficient information to classify it as a major or critical).

API Products List of Xunqiao API Site

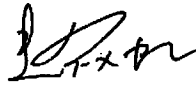
SN	Product	Product Code	Workshop
1.	Captopril	5104	I
		5103	
		5102	
		5101	
2.	Escitalopram Oxalate	5289	I&II&XIV
		5289	I&XIV
		5357	XIV
		5356	I&XIV
3.	Perindopril Tert-butylamine	5327	II&VIII
		5180&5653	
4.	Enalapril maleate	5324	XII
		5199	
		5112	
5.	Citalopram Hydrobromide	5360&5376	XIV
		5377	
		5291&5292	II
6.	Lisinopril	5124	III
		5122	
		5130	
7.	Iloperidone	5349	IV
8.	Olanzapine	5643	
9.	Desloratadine	5206	
10.	Paroxetine mesylate	5322	IV/XIV
11.	Voriconazole	5213	IX,VII,V&IV
		5207	VII,V&IV
12.	Ropinirole Hydrochloride	5600	IV&VII & IX
13.	Rivaroxaban	5364	V
14.	Lamotrigine	5630	
		5629	
15.	Torsemide	5623	
16.	Donepezil HCl (Pd Process)	5535	VII&V&IX
		5530&5666	II&V&IX

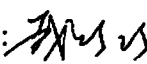
1 / 3

SN	Product	Product Code	Workshop
	Donepezil HCl (Pt Process)	5532	VII&V&IX
17.	Ramipril	5196	VII
		5654	
		5174	
		5654	
		5197	
18.	Quinapril Hydrochloride	5158	XII&VIII
		5156	
19.	Fosinopril Sodium	5151	VIII
		5157	
20.	Ketotifen Hydrogen Fumarate	5504	
		5508	
21.	Carvedilol	5334	
22.	Benazepril HCl	5141	
23.	Fexofenadine	5517	
		5516	
24.	Risperidone	5344	
		5342	
		5341	
25.	Aripiprazole	5169	XIII
		5667	
26.	Candesartan Cilexetil	5258&5259&5260	
		5251	
		5253	
		5668	
27.	Paroxetine HCl, Anhydrous	5306&5665	XIV
28.	Paroxetine HCl, Hemihydrate	5308&5670	
		5320&5669	
		5301	
29.	Duloxetine HCl	5281	
		5615	
		5618	IV
30.	Sertraline HCl	5319	XIV



SN	Product	Product Code	Workshop
31.	Quetiapine Fumarate	5611	II&XIV
		5611	XIV
		5612	

Prepared by/date: 
2018.09.11

Reviewed by/ Date: 
2018.09.11



浙江华海药业股份有限公司
ZHEJIANG HUAHAI PHARMACEUTICAL CO., LTD.

Page ID: 98639

Intermediate Products List of Xunqiao API Site

SN	Product	Product Code	Workshop
1.	ABP	5186	I
2.	Purified Fa	5106	
		5195	
3.	R-6 hydrochloride (Intermediate)	5150	VIII
4.	R-6 (Intermediate)	5153	
5.	L-6 (Intermediate)	5154	
6.	Benzyl ester p-toluenesulfonate salt (Intermediate)	5161	
7.	Ketotifen Methoxycarbinol (Intermediate)	5506	
8.	TPAB (Intermediate)	5640	IX
9.	NEPA-NCA of Enalapril (Intermediate)	5184	XII
10.	Enalapril Refided Hydride (Intermediate)	5115	
11.	N-methyl Paroxetine (Intermediate)	5318	XIV

Prepared by/date:

[Signature]
2018.09.11

Reviewed by/ Date:

[Signature]
2018.09.11

Intermediate synthesized
for in house use



Intermediate Products List of Xunqiao API Site

SN	API name	API Structure	Intermediate name	Intermediate Product Code	Workshop No.
1.	NA	NA	ABP	5186	Workshop I
2.	Captopril		Purified Fa	5106	
				5195	
3.	Fosinopril Sodium		R-6 hydrochloride (Intermediate)	5150	Workshop VIII
4.			R-6 (Intermediate)	5153	
5.			L-6 (Intermediate)	5154	
6.	Quinapril Hydrochloride		Benzyl ester p-toluenesulfonate salt (Intermediate)	5161	Workshop VIII
7.	Ketotifen Hydrogen Fumarate		Ketotifen Methoxycarbinol (Intermediate)	5506	
8.	Ertapenem		TPAB (Intermediate)	5640	Workshop IX
9.	Enalapril maleate		NEPA-NCA of Enalapril (Intermediate)	5184	Workshop XII
10.			Enalapril Refined Hydride (Intermediate)	5115	
11.	Paroxetine HCl		N-methyl Paroxetine (Intermediate)	5318	Workshop XIV

Prepared by/date:

2018.09.12

Reviewed by/ Date:

1/1

2018.09.12

API Products List of Chuannan Site

Workshop No.	Product Name	Production Area
Workshop 1	Losartan Potassium (Process II)	East Zone
Workshop 2	Valsartan	East Zone
Workshop 3	Losartan Potassium	East Zone
Workshop 4	Irbesartan	East Zone
Workshop 5	Nevirapine, anhydrous	East Zone
	Hydrochlorothiazide	East Zone
Workshop 7	Losartan Potassium (Process II)	East Zone
Workshop 9	Lisinopril Dihydrate	East Zone
Workshop 10	Irbesartan	East Zone
Workshop 12	Valsartan	East Zone
Workshop 13	Valsartan	East Zone
Workshop 16	Efavirenz	East Zone
Workshop 17	Irbesartan	East Zone
Workshop 18	Ranolazine	East Zone
	Levetiracetam (Process II)	East Zone
Workshop W02	Valsartan	West Zone
Workshop W03	Eprosartan Mesylate	West Zone
	Canagliflozin	West Zone
	Apixaban	West Zone
	Dabigatran Etexilate Mesylate	West Zone
	Nebivolol HCL	West Zone
Workshop W04	Febuxostat	West Zone



Workshop No.	Product Name	Production Area
	Topiramate	West Zone
	Clopidogrel Bisulfate	West Zone
	Ferric Citrate	West Zone
	Sucroferric Oxyhydroxide	West Zone
	Pioglitazone Hydrochloride	West Zone
	Levetiracetam (Process V)	West Zone
	Metroprolol Succinate	West Zone
	Terizidone	West Zone
Workshop W05	Telmisartan	West Zone
	Torsemide	West Zone
	Candesartan Cilexetil	West Zone
	Tadalafil	West Zone
	Olmesartan Medoxomil	West Zone
Workshop W06	Levodopa	West Zone
Workshop W07	Pregabalin	West Zone
Workshop W08		
Workshop W11 (Synthesis Area)	Levetiracetam (Process II)	West Zone
Workshop W17 (Clean Area)	Levetiracetam (Process II)	West Zone

Note: The products of above table are for commercial products.

Prepared by/ Date: *Chen Yi*
2018.09.04

Reviewed by/ Date: *Da: Babin*
2018.09.04



Intermediate Products List of Chuanan Site

Workshop No.	Product Name	Production Area
Workshop 1	Losartan Base	East Zone
Workshop 6	Trityl Losartan	East Zone
	2-n-Butyl-5-dimethylaminocarbonylmethyl-6-methyl-3-{2'-((N-triphenyl-methyl) tetrazol-5-yl) biphenyl-4-yl methyl} pyrimidin-4(3H)-one (DCMP)	East Zone
	Diethyl 2-(6-chloro-9H-Carbazol-2-yl)-2-methyl malonate	East Zone
	Losartan Base	East Zone
Workshop 7	Losartan Base	East Zone
Workshop 11	2-Chloro-3-amino-4-methyl pyridine	East Zone
	LVA30	East Zone
Workshop 12	N-[(2'-cyanobiphenyl-4-methyl)-[L]-valine methyl ester hydrochloride	East Zone
	N-[(2'-cyanobiphenyl-4-methyl)-[L]-valine methyl ester oxalate	East Zone
Workshop W05	TAD40	West Zone
	Trityl Olmesartan Medoxomil	West Zone

Note: LVA30 manufactured in Workshop 11 is made by ourselves and for internal use only.

Prepared by/ Date: Song King
 2018.09.04

Reviewed by/ Date: Da: Bmbin
 2018.09.04

PUBLIC ANALYST'S LABORATORY REPORT

Mr. Rory Mannion, Public Analyst.
Email: PALG.OMCL@hsc.ie
Telephone: (091) 581122
Fax: (091) 581212

Public Analyst's Laboratory,
University Hospital,
Scamuis Quirke Road,
Galway, Ireland.
08/10/2018

Lab Report Ref: P8-2018

Fedhmeannacht na Seirbhíse Sláinte
Health Service Executive

P.A.L. No.	HPRA No.	Supervising T.M.	Date received	Submitted by	Name of Product	Form of Product	Batch/Lot No.	Seal No.	Expiry Date	Manufacturing Date	µg NDMA per gram	µg Azide per gram
D87-2018	IN299.18	D. Costello	19/09/2018	Zhejiang Huahai Pharma	Valsartan API	Powder (API)	Batch No.: C5523-17-108	FA10280128	NA	21.02.2017	48.1	ND < 10
D88-2018	IN300.18	D. Costello	19/09/2018	Zhejiang Huahai Pharma	Valsartan API	Powder (API)	Batch No.: D5191-18-235	FA10280129	NA	27.08.2018	< 0.04	ND < 10
D89-2018	IN301.18	D. Costello	19/09/2018	Zhejiang Huahai Pharma	Valsartan API	Powder (API)	Batch No.: C5523-18-420	FA10280130	NA	04.08.2018	< 0.04	ND < 10
D90-2018	IN302.18	D. Costello	19/09/2018	Zhejiang Huahai Pharma	Valsartan API	Powder (API)	Batch No.: D5191-18-022	FA10280131	NA	17.03.2018	9.3	ND < 10

ND = Not Detected.

Comments: The Azide results reported above were obtained using an Ion Chromatography method based on the EP Monograph for the determination of Azide (Impurity B) in Irbesartan. The samples and standards were prepared in the OMCL section of this laboratory and the instrumental analysis was performed in the Water section of this laboratory.

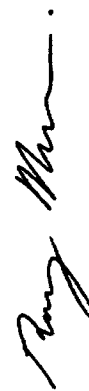
The NDMA (N-nitrosodimethylamine) results reported above were obtained using a Headspace GC-MS single quadrupole system. The samples and standards were prepared in the OMCL section of this laboratory and the instrumental analysis was performed in the Water section of this laboratory.

Note 1: This report shall not be reproduced, except in full, without written approval of the laboratory.

Note 2: This test report relates only to the sample tested.

Note 3: Any opinions and/or interpretations are outside the scope of accreditation.

* Denotes analysis included in laboratory scope of ISO 17025:2017 accredited tests



Rory Mannion
Public Analyst



Feidhmeannacht na Seirbhíse Sláinte
Health Service Executive

To: Richard Wanko, EDQM & AD-hoc Testing Group (Val)Sartan

From: Public Analysts Laboratory,
Seamus Quirke Road,
Galway, Ireland
353-91-542213 (Tel)
353-91-581212 (Fax)
declan.costello@hse.ie

Date: 5th October, 2018

Determination of N-Nitrosodimethylamine (NDMA) in Valsartan API received from Zhejiang Huahai Pharma.

1. Introduction

This report summarises the analysis and results of four Valsartan API samples received from Zhejiang Huahai Pharma on 19th September, 2018. The samples were obtained during a GMP inspection at the API manufacturing site, Zhejian Tianyu. The samples were analysed using an in-house developed and validated GC-MS (Headspace) method.

The method has an LOD of 0.04µg/g of NDMA.

Full method available on OMCL Extranet: <https://www.edqm.eu/sites/default/files/omcl-ndma-method-palq-ie-september2018.pdf>

2. Method (Quantification)

2.1 Headspace:

Oven Temp: 120°C
Sample Line Temp: 150°C
Transfer Line Temp: 150°C
Equilibrating Time: 10min

2.2 Column & Oven:

Column Oven Temp: 70°C
Injection Mode: Split
Split Ratio: 20
Column: Restek Rtx-624 (30m x 0.25mm ID, 1.4µm)

2.3 Reagents:

Dimethylsulfoxide (DMSO, Merck SupraSolv, for headspace gas chromatography)
Helium Gas (CP grade)
Reference Standard: N-Nitrosodimethylamine, Restek, 1000µg/mL in Methanol
QC Standard: N-Nitrosodimethylamine, Sigma-Aldrich, 200µg/mL in Methanol

2.4 Sample & Standard Preparation:

Tablets: 0.20-0.25g of Powdered Material; API: 0.05-0.20g
External standard additions:
Four aliquots of sample weighed into four separate headspace vials.
Vials spiked with 0, 2, 4 and 6µg of NDMA, respectively.
Analysed as per conditions described above.
Concentration of NDMA in samples obtained using the Standard Addition Curve.

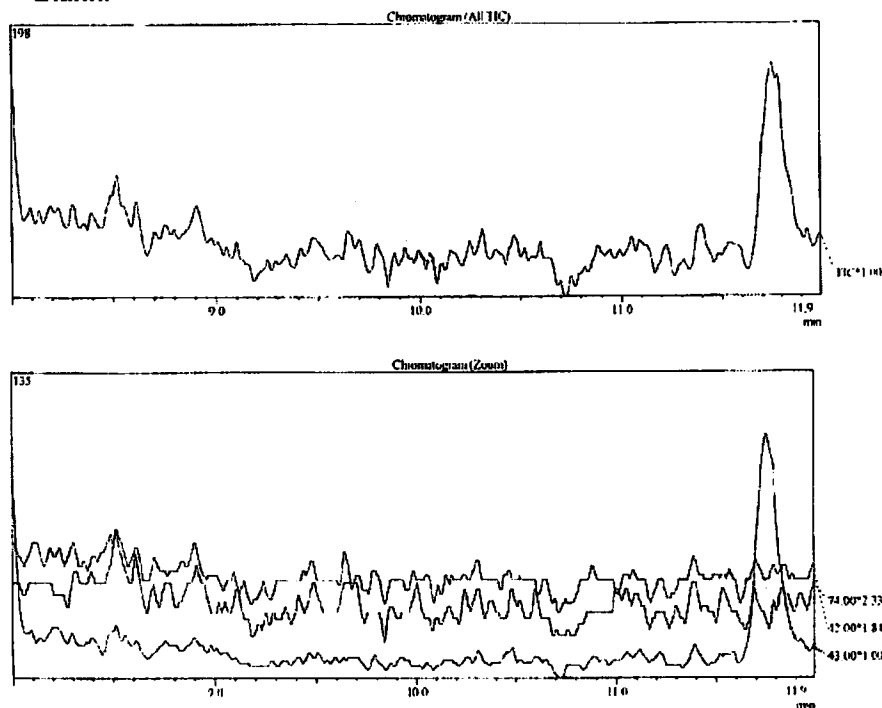
3. Sample Details and Results

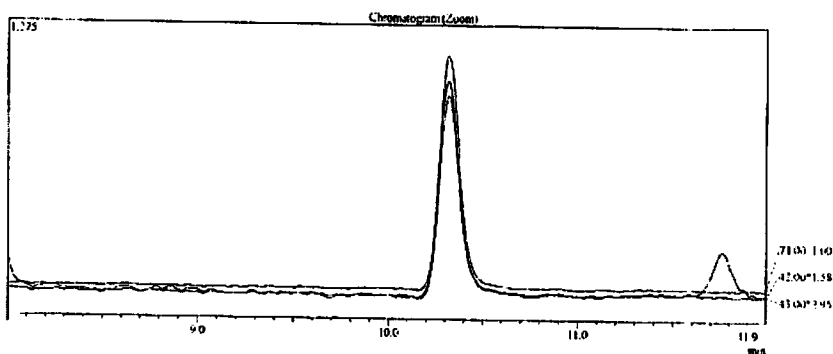
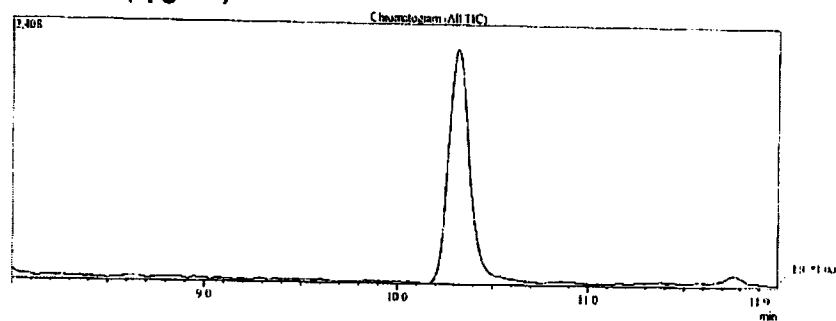
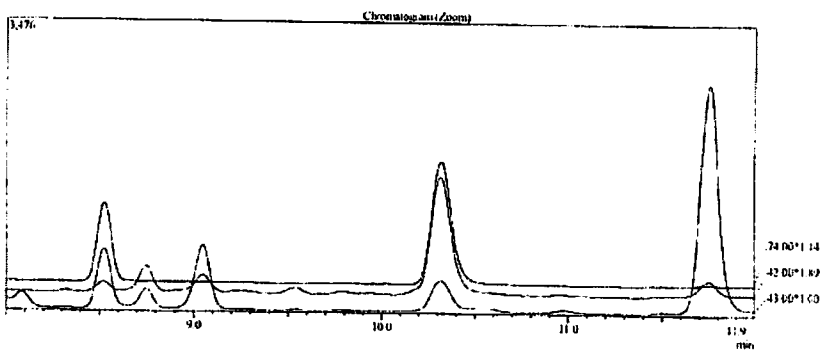
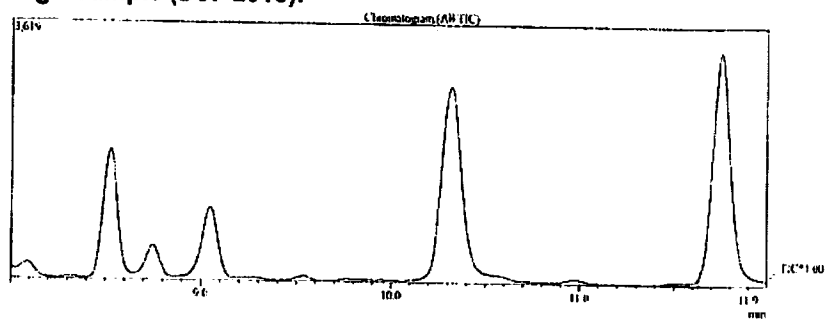
Sample No.	Sample Name	Batch	Result (µg/g)	ZH Results (µg/g)
D87-2018/IN299.18	Valsartan API	C5523-17-108	48.1	62.4
D88-2018/IN300.18	Valsartan API	D5191-18-235	<0.04	ND
D89-2018/IN301.18	Valsartan API	C5523-18-420	<0.04	ND
D90-2018/IN302.18	Valsartan API	D5191-18-022	9.3	8.8

ND = None Detected

4. Chromatographic Examples:

Blank:



Standard (2µg/mL):**High Sample (D87-2018):**

COMMERCIAL IN CONFIDENCE

**N-Nitroso-
dimethylamine
determination in
Valsartan APIs
Project 18/091**

**For The Medicines &
Healthcare products
Regulatory Agency**

Report No: MHRA/2018/059

1. Introduction

This report details the results of the analysis of Valsartan APIs. 6 API samples were received on the 17th of September 2018. On receipt at LGC the samples were registered and put into appropriate storage prior to analysis.

The samples were analysed for:

- N-Nitrosodimethylamine by LC-MS

2. Methods

Nitrosodimethylamine by LC-UV-MS

Method adapted from the 'Second Pharma Co. Ltd' method for the analysis of N-Nitrosodimethylamine (NDMA) in Valsartan APIs.

Column: Phenomenex, Gemini-NX, C18, 250 x 4.6 mm, 5 µm

Mobile phase – A: Water : Methanol (80:20 v/v)

Mobile phase – B: Methanol

Gradient:

Time (minutes)	M.P.-A (%)	M.P.-B (%)
0	100	0
13	100	0
13.1	30	70
18.0	30	70
18.1	100	0
27	100	0

Flow rate 1.0 mL/min

Run time 27 minutes

Oven temperature 30 °C

Tray temperature 10 °C

Injection volume 25 µL

Solutions for API Analysis

Internal Standard Soln. Nitrosodimethylamine-d6 (NDMA-d6, 1000 µg/mL, Restek, lot A0135511) diluted to 0.5 µg/mL in methanol. (10 µg/mL solution used for high range samples).

Standard Solns. N-Nitrosodimethylamine (NDMA 200 µg/ml, Supleco, lot XA25624V, RT/V/0029) solutions prepared between 0.005 µg/mL and 0.1 µg/mL in 20% methanol, also containing 0.1 µg/mL of internal standard.

Test Soln. 1 g of API weighed into centrifuge tube. 2 mL of internal standard solution added. Solution mixed and sonicated to dissolve the API. 8 mL of water added to tube whilst gently vortex mixing. The tube was then centrifuged at 3000 rpm for 15 minutes, and the supernatant injected on the chromatographic system.

For higher level samples (circa 100 ppm): 50 mg of API was weighed into centrifuge tube, then 1 mL of methanol added and 1 mL of 10 µg/mL internal standard solution. Solution mixed and sonicated to dissolve the API. 8 mL of water was added to tube whilst gently vortex mixing.

The tube was then centrifuged at 3000 rpm for 15 minutes, and the supernatant diluted 1 mL to 10 mL with 20% methanol.

Mass Spectrometric Parameters

MS: Thermo LCQ Fleet – Ion trap MS
Source ionisation: +ve APCI
Vaporization Temp: 300 °C
Source Current 15 µA
Capillary/Transfer Temp 250 °C
Sheath Gas 40
Mass Detection SIM: 75 m/z for NDMA
SIM: 81 m/z for NDMA-d6 (internal standard)

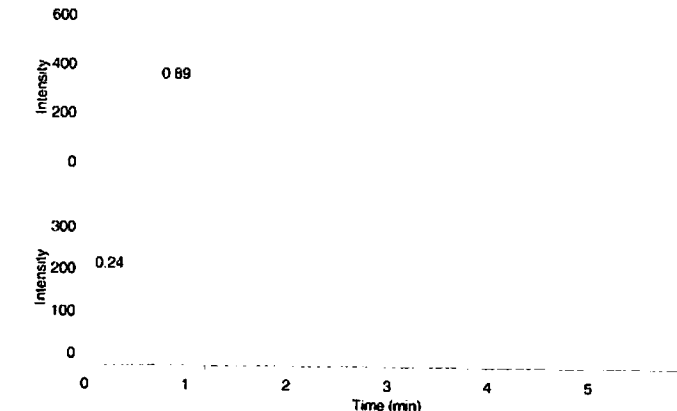
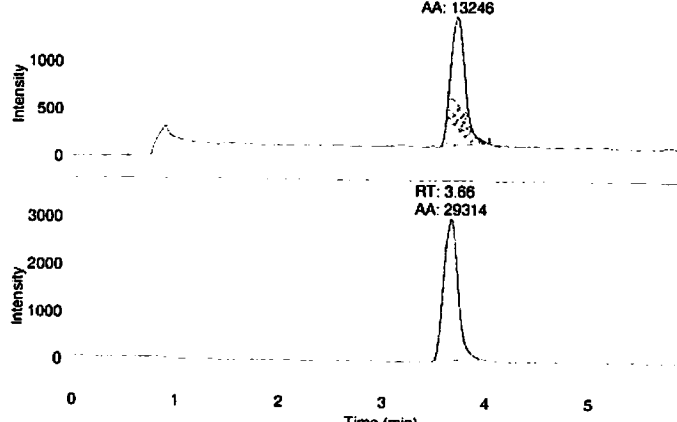
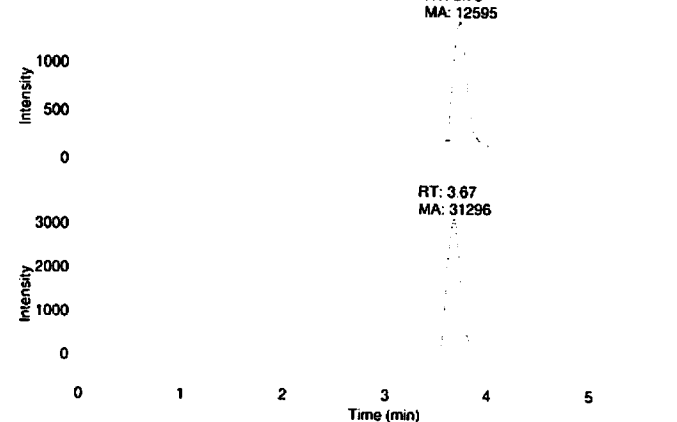
3. Sample Details

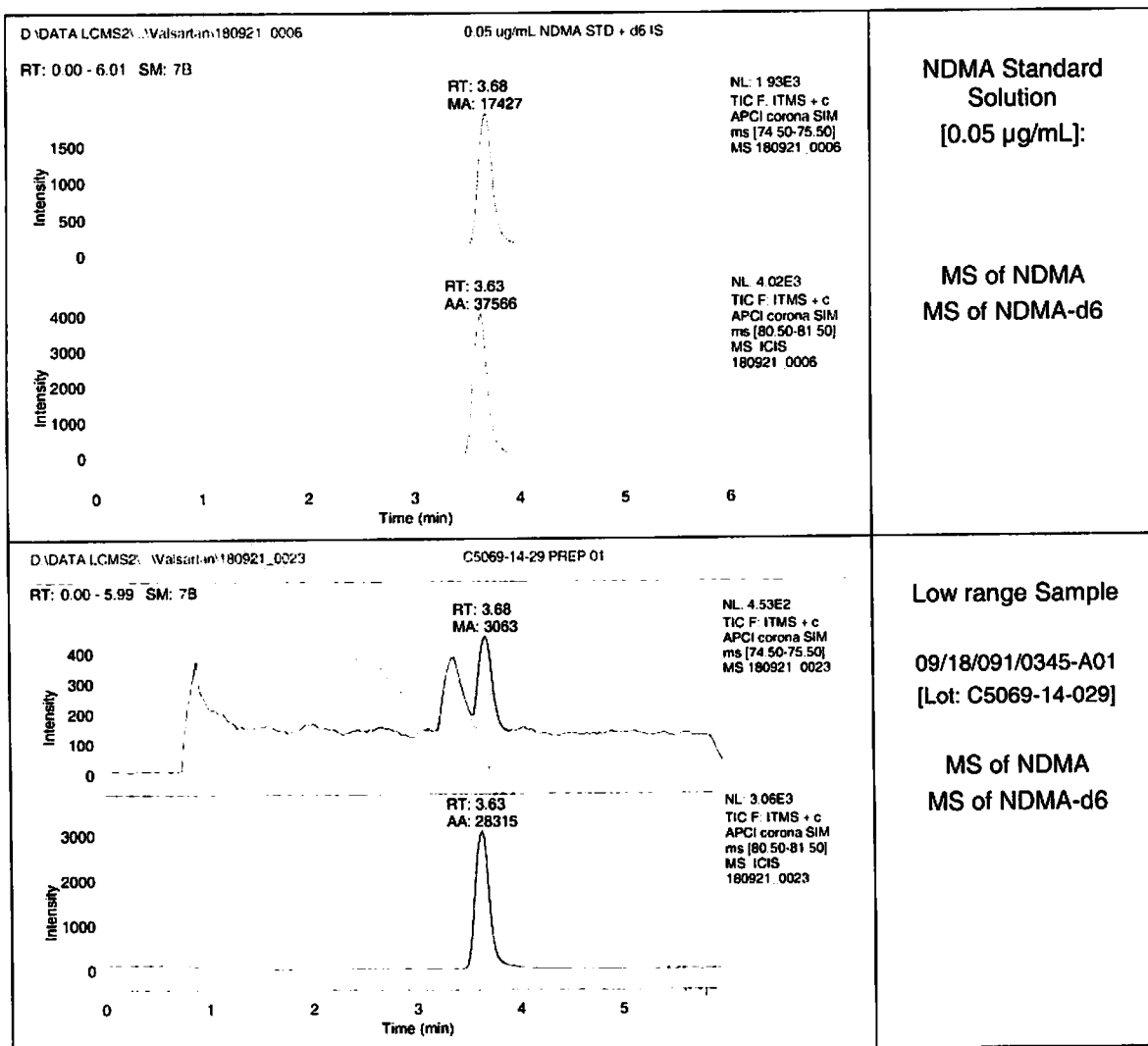
MTS Ref 09/18/091/	Form	Manufacturer	Lot Number	Expiry
0344-A01	API	Z.Huahai	C5271-17-288	-
0345-A01	API	Z.Huahai	C5069-14-029	-
0346-A01	API	Z.Huahai	C5355-17-097	-
0347-A01	API	Z.Huahai	C5355-16-332	-
0348-A01	API	Z.Huahai	C5523-17-374M	-
0349-A01	API	Z.Huahai	C5523-17-696	-

4. Results

MTS Ref 09/18/091/	NDMA ppm (µg/g) (21/09/2018 – 25/09/2018)	Z.Huahai test result ppm (µg/g)
0344-A01	93.8, 99.3 Mean = 96.6	Not Detected (result out-of-trend)
0345-A01	0.11, 0.11 Mean = 0.11	Not Detected
0346-A01	86.8, 85.9 Mean = 86.3	Not Tested
0347-A01	104.5, 106.9 Mean = 105.7	111.6
0348-A01	92.6, 88.7 Mean = 90.6	78.7
0349-A01	61.7, 61.8 Mean = 61.7	62.7

5. Chromatograms

<p>D:\Data LCMS2\180826_Valsartan001</p> <p>Blank</p> <p>RT: 0.00 - 6.00 SM: 7B</p>  <p>NL: 3.24E2 TIC F: ITMS + c APCI corona SIM ms [74.50-75.50] MS 180826_Valsartan0 01</p> <p>NL: 1.91E2 TIC F: ITMS + c APCI corona SIM ms [80.50-81.50] MS 180826_Valsartan0 01</p>	<p>Blank</p> <p>MS of NDMA MS of NDMA-d6</p>
<p>D:\Data LCMS2\180826_Valsartan011</p> <p>NDMA - NDMA-d6 0.05ug/mL STD</p> <p>RT: 0.00 - 5.99 SM: 7B</p>  <p>RT: 3.71 AA: 13246</p> <p>NL: 1.50E3 TIC F: ITMS + c APCI corona SIM ms [74.50-75.50] MS ICIS 180826_Valsartan0 1</p> <p>RT: 3.66 AA: 29314</p> <p>NL: 3.01E3 TIC F: ITMS + c APCI corona SIM ms [80.50-81.50] MS ICIS 180826_Valsartan0 1</p>	<p>NDMA Standard Solution [0.05 µg/mL]:</p> <p>MS of NDMA MS of NDMA-d6</p>
<p>D:\Data LCMS2\180826_Valsartan005</p> <p>18091034601 Prep 01</p> <p>RT: 0.00 - 5.99 SM: 7B</p>  <p>RT: 3.73 MA: 12595</p> <p>NL: 1.47E3 TIC F: ITMS + c APCI corona SIM ms [74.50-75.50] MS 180826_Valsartan0 05</p> <p>RT: 3.67 MA: 31296</p> <p>NL: 3.16E3 TIC F: ITMS + c APCI corona SIM ms [80.50-81.50] MS 180826_Valsartan0 05</p>	<p>Typical High range Sample</p> <p>09/18/091/0346-A01 [Lot: C5355-17-097]</p> <p>MS of NDMA MS of NDMA-d6</p>



6. Discussion

The NDMA results for the API samples were similar to those provided by the manufacturer, with the exception of 09/18/091/0344-A01 (lot: C5271-17-288). The result supplied with this sample was declared as 'Not Detected', but it was noted that this result was 'out-of-trend' with comparable batches. Our results showed that this sample contained NDMA at an average level of 96.6 ppm.